Προεγχειρητικός Καρδιολογικός Έλεγχος σε Επεμβάσεις Περιφερεικών Αγγείων

Τσεκούρα Δωροθέα
Καρδιολόγος
Αρεταίειο Νοσοκομείο
Ειδικό Διδακτικό Προσωπικό ΕΚΠΑ

10/10/2018
Tissue injury

Stress response
- Tachycardia
- Hypertension

Prothrombotic factors
- Fibrinogen, PLT activation and aggregation

↑ myocardial oxygen demand

Myocardial ischemia

Heart failure
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

11.2.2. Coronary artery disease in patients presenting with peripheral arterial diseases

11.2.2.1. Coronary artery disease in patients with carotid artery stenosis

In a study including 276 patients with non-cardioembolic ischaemic stroke/TIA, coronary CTA detected coronary stenosis (>50%) in 18% of cases. The prevalence was 4-fold higher in the case of carotid stenosis >50%. In a prospective investigation of 390 patients undergoing elective CAS, systematic coronary angiography found coronary artery stenosis >70% in 61% of cases.

In the case of severe carotid artery stenosis, the presence of associated CAD requires prioritization of revascularization according to the patient's clinical status and to the severity of carotid and coronary disease. Carotid revascularization should be performed first only in the case of unstable neurological symptoms; asymptomatic carotid stenosis should be treated, whenever appropriate, following CAD revascularization.

11.2.2.2 Coronary artery disease in patients undergoing vascular surgery of lower limbs

In patients undergoing surgery for LEAD, the probability of significant concomitant CAD at coronary angiography is ~50–60%. For the management of these patients, aortic and major vascular surgery are classified as 'high risk' for cardiac complications, with an expected 30-day MACE rate (cardiac death and MI) >5%. The management of CAD in patients requiring vascular surgery should be based on the 2014 ESC/ESA Guidelines on non-cardiac surgery.
<table>
<thead>
<tr>
<th>Low-risk: &lt; 1%</th>
<th>Intermediate-risk: 1–5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Superficial surgery</td>
<td>• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy</td>
</tr>
<tr>
<td>• Breast</td>
<td>• Carotid symptomatic (CEA or CAS)</td>
</tr>
<tr>
<td>• Dental</td>
<td>• Peripheral arterial angioplasty</td>
</tr>
<tr>
<td>• Endocrine: thyroid</td>
<td>• Endovascular aneurysm repair</td>
</tr>
<tr>
<td>• Eye</td>
<td>• Head and neck surgery</td>
</tr>
<tr>
<td>• Reconstructive</td>
<td>• Neurological or orthopaedic: major (hip and spine surgery)</td>
</tr>
<tr>
<td>• Carotid asymptomatic (CEA or CAS)</td>
<td>• Urological or gynaecological: major</td>
</tr>
<tr>
<td>• Gynaecology: minor</td>
<td>• Renal transplant</td>
</tr>
<tr>
<td>• Orthopaedic: minor (menisectomy)</td>
<td>• Intra-thoracic: non-major</td>
</tr>
<tr>
<td>• Urological: minor (transurethral resection of the prostate)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-risk: &gt; 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aortic and major vascular surgery</td>
</tr>
<tr>
<td>• Open lower limb revascularization or amputation or thromboembolectomy</td>
</tr>
<tr>
<td>• Duodeno-pancreatic surgery</td>
</tr>
<tr>
<td>• Liver resection, bile duct surgery</td>
</tr>
<tr>
<td>• Oesophagectomy</td>
</tr>
<tr>
<td>• Repair of perforated bowel</td>
</tr>
<tr>
<td>• Adrenal resection</td>
</tr>
<tr>
<td>• Total cystectomy</td>
</tr>
<tr>
<td>• Pneumonectomy</td>
</tr>
<tr>
<td>• Pulmonary or liver transplant</td>
</tr>
</tbody>
</table>
Figure 8  Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease. The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g., in patients with CAD, 5 - 9% of cases have concomitant carotid stenosis >70%). ABI = ankle-brachial index; CAD = coronary artery disease; LEAD = lower extremity artery disease; RAS = renal artery stenosis.
A stepwise approach

Step 1: Urgent surgery

Step 2: Active or unstable cardiac conditions

Step 3: What is the risk of the surgical procedure?

Step 4: What is the functional capacity of the patient?

Step 5: In patients with poor low functional capacity: consider the risk of surgical procedure

Step 6: Consider cardiac risk factors

Step 7: Consider non invasive testing
Step 1 - Urgent surgery

NO

Step 2

YES

Surgery

Patient or surgical specific factors dictate the strategy and do not allow further cardiac testing: the consultant provides recommendations on peri-operative management, surveillance for cardiac events and continuation of chronic CV medical treatment.

doi:10.1093/eurheartj/ehu282
A stepwise approach

Step 1: Urgent surgery

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Step 6: Consider cardiac risk factors

Step 7: Consider non invasive testing
Step 2 - Active or unstable cardiac condition(s):

- Unstable angina pectoris
- Acute heart failure
- Significant cardiac arrhythmias
- Symptomatic valvular heart disease
- Recent myocardial infarction\(^3\) and residual myocardial ischemia

Yes

- Postpone the procedure
- Treatment options should be discussed in a multi-disciplinary team involving all peri-operative care physicians

Surgery

European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu282
A stepwise approach

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European Heart Journal (2014) 35, 2383–2431
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### Step 3 - Risk of surgical procedure: 30-day CV death and MI

<table>
<thead>
<tr>
<th>Low-risk: &lt; 1%</th>
<th>Intermediate-risk: 1-5%</th>
<th>High-risk: &gt; 5%</th>
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</thead>
<tbody>
<tr>
<td>• Superficial surgery</td>
<td>• Intra-abdominal: splenectomy, hiatal hernia repair, cholecystectomy</td>
<td>• Aortic and major vascular surgery</td>
</tr>
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</table>
Step 3 - Risk of surgical procedure

Low risk (<1%) of surgical procedure
Identify risk factors and provide recommendations on lifestyle and medical treatment according to relevant ESC guidelines

Intermediate or High Risk of surgical procedure

Step 4

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tr>
<td>In patients with known IHD or myocardial ischaemia, initiation of a titrated low-dose beta-blocker regimen may be considered before surgery.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In patient with heart failure and systolic dysfunction, ACEI should be considered before surgery.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>In patients undergoing vascular surgery, initiation of statin therapy should be considered.</td>
<td>IIA</td>
<td>B</td>
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Surgery

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European Heart Journal (2014) 35, 2383–2431
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A stepwise approach

Step 1: Urgent surgery

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Step 6: Consider cardiac risk factors

Step 7: Consider non invasive testing

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European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu282
Step 4 - Functional capacity of the patient scheduled for intermediate or high-risk surgery

Functional Capacity

1 MET
Can you...
Take care of yourself? Eat, dress, or use the toilet?
Walk indoors around the house?
Walk 100 m on level ground at 3 to 5 km per h?

4 METs
Can you...
Climb two flights of stairs or walk up a hill?
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

Greater than 10 METs
**Step 4** - Functional capacity of the patient scheduled for intermediate or high-risk surgery

- **Good (≥4 METS)**
- **Moderate or poor (<4 METS)**

**Step 5**

**Recommendations**

<table>
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**Surgery**

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European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu232
A stepwise approach

Step 1: Urgent surgery

Step 2: Active or unstable cardiac conditions

Step 3: What is the risk of the surgical procedure?

Step 4: What is the functional capacity of the patient?

Step 5: In patients with poor low functional capacity: consider the risk of surgical procedure

Step 6: Consider cardiac risk factors

Step 7: Consider non invasive testing
Step 5 - In patients with functional capacity <4 METS consider risk of surgery

Intermediate risk surgery

High risk surgery

Step 6

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with one or more clinical risk factors non-invasive testing may be considered.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In patients with one or more clinical risk factors baseline ECG is recommended.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu282
A stepwise approach

Step 1: Urgent surgery

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Step 6: Consider cardiac risk factors

Step 7: Consider non invasive testing
Step 6
Clinical risk factors

- Ischaemic heart disease (angina pectoris and/or previous myocardial infarction)
- Heart failure
- Stroke or transient ischaemic attack
- Renal dysfunction (serum creatinine >170 μmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min/1.73 m²)
- Diabetes mellitus requiring insulin therapy

* According to the universal definition of myocardial infarction
Step 6
Cardiac risk factors in high-risk surgery

1. Ischaemic heart disease
2. Heart failure
3. Stroke or TIA
4. Renal dysfunction
5. Diabetes mellitus

Number of risk factors $\leq 2$
Rest echocardiography and biomarkers for evaluation of LV function may be considered.

Class IIb
Level B-C

Number of risk factors $\geq 3$

Surgery

Step 7
A stepwise approach

Step 1: Urgent surgery
Step 2: Active or unstable cardiac conditions
Step 3: What is the risk of the surgical procedure?
Step 4: What is the functional capacity of the patient?
Step 5: In patients with poor low functional capacity: consider the risk of surgical procedure
Step 6: Consider cardiac risk factors
Step 7: Consider non invasive testing
Step 7 – Pre-operative testing

Consider also for patient counselling, surgery, and anaesthesia technique

- Cardiac stress test
  - Extensive ischaemia
    - An individualized peri-operative management is recommended considering the potential benefit of the proposed surgical procedure compared with the predicted adverse outcome, and the effect of medical therapy and/or coronary revascularization
  - No or moderate stress-induced ischaemia
    - Surgery

Step 7b
Step 7b
Extensive stress induced ischaemia

Cardiac stress test
- Individualized management
  - Benefit of the procedure
  - Predicted adverse outcome
  - Effect of medication and revascularization

Extensive ischaemia

- Balloon angioplasty: Surgery can be performed >2 weeks after intervention with continuation of aspirin treatment.
- Bare-metal stent: Surgery can be performed >4 weeks after intervention. Dual antiplatelet therapy should be continued for at least 4 weeks.
- Surgery can be performed within 12 months after intervention for old-generation DES and within 6 months for new-generation DES.
- CABG

Surgery

Continuation or discontinuation of aspirin in patients previously treated with aspirin may be considered in the peri-operative period, and should be based on an individual decision that depends on the peri-operative bleeding risk weighed against the risk of thrombotic complications.

European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu282

www.escardio.org/guidelines
**Preoperative evaluation**

- **Non invasive tests**
  - ECG
  - Echo
  - Stress test
  - MRI
  - CT
  - CPET

- Ischaemic heart disease (angina pectoris and/or previous myocardial infarction)
- Heart failure
- Stroke or transient ischaemic attack
- Renal dysfunction (serum creatinine >170 μmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min/1.73 m²)
- Diabetes mellitus requiring insulin therapy

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*European Heart Journal (2014) 35, 2383–2431*
## Preoperative Evaluation

- **Invasive tests**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative angiography is recommended in patients with proven myocardial ischaemia and unstabilized chest pain (Canadian Cardiovascular Society Class III–IV) with adequate medical therapy requiring non-urgent, non-cardiac surgery.</td>
<td>I</td>
<td>C</td>
<td>56,72</td>
</tr>
<tr>
<td>Pre-operative angiography may be considered in stable cardiac patients undergoing non-urgent carotid endarterectomy surgery.</td>
<td>IIb</td>
<td>B</td>
<td>76</td>
</tr>
<tr>
<td>Pre-operative angiography is not recommended in cardiac-stable patients undergoing low-risk surgery.</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

*European Heart Journal (2014) 35, 2383–2431*
Risk reduction strategies

- Pharmacological
  - β Blockers
  - Statins
  - Nitrates
  - Angiotensin-converting enzyme inhibitor
  - Calcium channel blockers
  - Ivabradine
  - α2 Receptor agonists
  - Diuretics
  - Antiplatelet medication
  - Anticoagulant therapy

- Revascularization

*European Heart Journal (2014) 35, 2383–2431*
# Antiplatelet medication

- Aspirin
- Ticlopidin
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor
- Triflusal
- Dipyridamole

ESC guidelines European Heart Journal 2017, doi:10.1093/eurheartj/ehp337
Management of antiplatelet therapy in carotid artery stenosis

Asymptomatic

Carotid Artery Stenting

Carotid Surgery

SAPT^a, Class IA

SAPT^a, Class Ib/C

DAPT A/C, Class Ib/C

SAPT^a, Class Ib/C

ESC guidelines European Heart Journal 2017 doi: 10.1093/eurheartj/ehx095
## ESC recommendations on peri-operative aspirin use

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation of aspirin in patients previously treated with aspirin may be considered in the peri-operative period (based on risk of bleeding and thrombosis).</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Discontinuation of aspirin in patients previously treated with that drug should be considered in patients in whom haemostasis is anticipated to be difficult to control during surgery.</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>
Practical approaches in patients taking dual-antiplatelet therapy

In surgical procedures with high to very high bleeding risk:

(i) stop clopidogrel 5 days before surgery and stay on ASA, unless very high bleeding risk surgery;
(ii) if prasugrel is used, therapy should be stopped 7 days before surgery based on its prolonged and less unpredictable action compared with clopidogrel;
(iii) the advantage of ticagrelor in patients referred for surgery would be its fast offset of action after stopping intake. In the PLATElet inhibition and clinical Outcomes (PLATO) trial, ticagrelor was stopped 3–5 days before CABG and perioperative bleeding rate was broadly similar to that seen with clopidogrel;
(iv) the substitution of combined antiplatelet therapy with LMWH or UFH alone is ineffective;
(v) restart clopidogrel (prasugrel and ticagrelor) as soon as possible with loading dose (if possible < 24 h after operation);
(vi) in very high-risk patients, in whom cessation of antiplatelet therapy before surgery seems to be dangerous (e.g. shortly after stent implantation), it has been suggested that to switch from clopidogrel 5 days before surgery to a short half-life antiplatelet agent, e.g. the GPlIb/IIIa-inhibitor tirofiban, and stop infusion of these agents 4 h before surgery. This strategy has, however, not been investigated in prospective randomized trials.

Management of patients on DAPT who are referred for surgical procedures involves consideration of:

(1) the risk of stent thrombosis (particularly if DAPT needs to be interrupted);
(2) the consequences of delaying the surgical procedure; and
(3) the increased intra- and periprocedural bleeding risk and possible consequences of such bleeding if DAPT is continued
Table 1. Thrombotic risk definition.

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 months after PCI with BMS</td>
<td>&gt;1 month &lt;6 months after PCI with BMS</td>
<td>&lt;1 month after PCI with BMS</td>
</tr>
<tr>
<td>&gt;12 months after PCI with DES</td>
<td>&gt;6 &lt;12 months after PCI with DES</td>
<td>&lt;6 months after PCI with DES</td>
</tr>
<tr>
<td></td>
<td>&gt;12 months after complex PCI with DES (long stents, multiple</td>
<td>&lt;12 months after complex PCI with DES (long stents, multiple</td>
</tr>
<tr>
<td></td>
<td>stents, overlapping, small vessels, bifurcations, left main,</td>
<td>stents, overlapping, small vessels, bifurcations, left main, last</td>
</tr>
<tr>
<td></td>
<td>last remaining vessel)</td>
<td>remaining vessel)</td>
</tr>
</tbody>
</table>

PCI in ACS, previous stent thrombosis, LVEF <35%, chronic renal failure and diabetes mellitus increase the thrombotic risk. Use of second-generation DES might reduce the thrombotic risk. Patients submitted to CABG or with ACS medically treated are considered at high risk in the first month, at intermediate risk between the 1st and 6th month, and at low risk after 6 months. Patients treated with POBA are considered at high risk within the first 2 weeks, at intermediate risk between 2 and 4 weeks, and at low risk after 4 weeks. ACS: acute coronary syndrome; BMS: bare metal stent; CABG: coronary artery bypass graft; DES: drug-eluting stent; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty.
Table 4. Vascular surgery.

<table>
<thead>
<tr>
<th>Vascular Procedure</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy,</td>
<td>ASA: continue</td>
<td>ASA: continue</td>
<td>ASA: continue</td>
</tr>
<tr>
<td>bypass or endarterectomy of</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
</tr>
<tr>
<td>lower extremity, EVAR, TEVAR, limb</td>
<td>- Discontinue 5 days before*</td>
<td>- Consider PTA or stenting</td>
<td>- Elective surgery: postpone at least 30 days after PCI</td>
</tr>
<tr>
<td>amputations</td>
<td>- Resume within 24-72 hours, with a loading dose</td>
<td>- ASA: continue</td>
<td>- ASA: continue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors: continue</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors: continue</td>
</tr>
<tr>
<td>Haemorrhagic risk</td>
<td>Open abdominal aorta surgery</td>
<td>ASA: continue</td>
<td>ASA: continue</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
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<td>- Discontinue 5 days before*</td>
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<td>- Resume within 24-72 hours, with a loading dose</td>
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<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors: continue</td>
</tr>
<tr>
<td>High risk</td>
<td>Open thoracic and thoracoabdominal surgery</td>
<td>ASA: discontinue</td>
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</tr>
<tr>
<td></td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors:</td>
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<td></td>
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<td></td>
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<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitors: continue</td>
</tr>
</tbody>
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* 7 days prior for prasugrel; References 90-98. ASA: aspirin; EVAR: endovascular repair for aortic aneurysm; PCI: percutaneous coronary intervention or coronary angioplasty; PTA: percutaneous transluminal angioplasty; TEVAR: thoracic endovascular aortic/aneurysm repair.
In surgical procedures with low bleeding risk, every effort should be taken not to discontinue DAPT perioperatively.

In surgical procedures with moderate bleeding risk, patients should be maintained on aspirin while P2Y$_{12}$ inhibitor therapy should be discontinued whenever possible.

More challenging decision making is to be faced among patients on DAPT who undergo high bleeding risk non-cardiac surgeries, including vascular reconstructions, complex visceral procedures, neurosurgery, and transbronchial operations. In these cases, particular attention should be paid to timely discontinuation of P2Y$_{12}$ inhibitor therapy to minimize the off-therapy period before surgical intervention.

*European Hear Journal 2017,* [https://doi.org/10.1093/eurheartj/ehx419](https://doi.org/10.1093/eurheartj/ehx419)
Antiplatelet medication


10/10/2018
For patients with a very high risk of stent thrombosis,

- bridging therapy with intravenous, reversible glycoprotein inhibitors, such as eptifibatide or tirofiban, should be considered.
- Cangrelor, the new reversible intravenous P2Y12-inhibitor, has been shown to provide effective platelet inhibition but is not yet available.
- The use of low-molecular-weight heparin (LMWH) for bridging in these patients should be avoided.

Dual anti-platelet therapy should be resumed as soon as possible after surgery and, if possible, within 48 hours.
In summary, it is recommended that DAPT be administered for at least

- 1 month after BMS implantation in stable CAD,
- for 6 months after new-generation DES implantation and
- for up to 1 year in patients after ACS, irrespective of revascularization strategy.

Importantly, a minimum of 1 (BMS) to 3 (new-generation DES) months of DAPT might be acceptable, independently of the acuteness of coronary disease, in cases when surgery cannot be delayed for a longer period; however, such surgical procedures should be performed in hospitals where 24/7 catheterization laboratories are available, so as to treat patients immediately in case of peri-operative atherothrombotic events.

Independently of the timeframe between DES implantation and surgery, single anti-platelet therapy (preferably with aspirin) should be continued.
P2Y<sub>12</sub> inhibitor interruption after PCI for elective non-cardiac surgery<sup>1</sup>

ACS at index PCI or other high ischaemic risk features?<sup>2</sup>

- Time from DAPT initiation
  - No
    - 1 mo.
      - Class III B
      - Class IIla B
      - Class I B
  - Yes
    - 6 mo.
      - Class III B
      - Class IIlb C
      - Class I B

---

**Figure 8** Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = IIa; orange = Class IIb).

ACS = acute coronary syndromes.

<sup>1</sup>Availability of H24 cath-lab service in place is suggested in case of major surgery within 6 months after PCI.

<sup>2</sup>High ischaemic risk features are presented in Table 5.

**Table 5** High-risk features of stent-driven recurrent ischaemic events

- Prior stent thrombosis on adequate antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease especially in diabetic patients
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
- At least three stents implanted
- At least three lesions treated
- Bifurcation with two stents implanted
- Total stent length >60 mm
- Treatment of a chronic total occlusion

---

ESC guidelines European Heart Journal 2017 doi: 10.1093/eurheartj/ehx095
<table>
<thead>
<tr>
<th></th>
<th>Tirofiban</th>
<th>Eptifibatide</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of action</strong></td>
<td>Immediate</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>Potent platelet inhibition</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Plasma half-life</strong></td>
<td>2 h</td>
<td>2.5 h</td>
<td>3-5 min</td>
</tr>
<tr>
<td><strong>Offset of action</strong></td>
<td>4-6 h</td>
<td>4-6 h</td>
<td>1 h</td>
</tr>
<tr>
<td><strong>P2Y&lt;sub&gt;12&lt;/sub&gt; specific</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dose (no bolus)</strong></td>
<td>0.1 µg/kg/min (0.05 µg/kg/min for creatinine clearance &lt;50 ml/min)</td>
<td>2.0 µg/kg/min (1.0 µg/kg/min for creatinine clearance &lt;50 ml/min)</td>
<td>0.75 µg/kg/min (does not require dose adjustment with impaired renal function)</td>
</tr>
</tbody>
</table>

*IV = intravenous.*
Proposed Perioperative IV Antiplatelet Bridging Strategies

With small-molecule GPIb/IIIa inhibitors

- Low dose aspirin continued throughout
- START small molecule CPI (tirofiban, eptifibatide)
- STOP small molecule CPI (tirofiban, eptifibatide)
- STOP prasugrel
- STOP clopidogrel
- Surgery
- RESUME small molecule CPI* (tirofiban, eptifibatide)
- RESUME clopidogrel***

** Tiroliban: 0.1 mcg/kg/min; if creatinine clearance <50 mL/min, adjust to 0.05 mcg/kg/min. Eptifibatide: 2.0 mcg/kg/min; if creatinine clearance is <50 mL/min, adjust to 1.0 mcg/kg/min.
*** With 300-500 mg loading dose, as soon as oral administration not possible.

With Cangrelor

- Low dose aspirin continued throughout
- START cangrelor**
- STOP prasugrel
- STOP clopidogrel
- STOP cangrelor
- Surgery
- RESUME cangrelor***

** Initiate within 72 hours from P2Y12 inhibitor discontinuation at a dose of 0.75 mg/kg/min for a minimum of 48 hours and a maximum of 7 days.
*** With 300-500 mg loading dose, as soon as oral administration not possible.

Description of short-acting intravenous antiplatelet drug regimen that could be used for perioperative bridging. GP = glycoprotein; IV = intravenous.
# Dual antiplatelet therapy in patients undergoing elective non-cardiac surgery

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>After coronary stent implantation, elective surgery requiring discontinuation of the P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Discontinuation of P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel, and at least 7 days for prasugrel.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

---

In patients with recent MI or other high ischaemic risk features requiring DAPT, elective surgery may be postponed for up to 6 months.

If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.

It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.

---

**DAPT** = dual antiplatelet therapy; MI = myocardial infarction.

*Class of recommendation.

Level of evidence.

High ischaemic risk features are provided in Table 5.
Anticoagulant therapy

- Warfarin
- Dabigadran
- Rivaroxaban
- Abixaban
- Edoxaban

Non-vitamin K antagonist Oral AntiCoagulants (NOACs)
Anticoagulant therapy

- Warfarin
<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Indication for VKA Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Mechanical Heart Valve</td>
</tr>
<tr>
<td></td>
<td>Any mitral valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>Any caged-ball or tilting disc aortic valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>Recent (within 6 mo) stroke or transient ischemic attack</td>
</tr>
<tr>
<td></td>
<td>Rheumatic valvular heart disease</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age &gt; 75 y</td>
</tr>
<tr>
<td></td>
<td>Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation)</td>
</tr>
<tr>
<td></td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</td>
</tr>
</tbody>
</table>

CHADS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.

High-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a CHADS₂ score < 5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Suggested Risk Stratification: Mechanical Heart Valves

**High Risk**
- Any mitral valve prosthesis
- Older (caged-ball or tilting disc) aortic valve prosthesis
- Recent (within 6 months) stroke or TIA

**Moderate Risk**
- Bileaflet aortic valve and at least one of:
  - Atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 years

**Low Risk**
- Bileaflet aortic valve without atrial fibrillation and no other risk factors for stroke
# CHA₂DS²-Vasc score

One point for each of the following criteria:

- congestive heart failure
- arterial hypertension
- diabetes mellitus
- age 65 or above
- vascular disease
- female sex

Two points for:

- age 75 or above
- history of stroke

<table>
<thead>
<tr>
<th>CHA₂DS₂-Vasc score points</th>
<th>Stroke risk % per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Suggested Risk Stratification: Atrial Fibrillation

High Risk
- CHADS$_2$ score = 5-6
- Recent (within 3 months) stroke or TIA
- Rheumatic valvular heart disease

Moderate Risk
- CHADS$_2$ score = 3-4

Low Risk
- CHADS$_2$ score = 0-2 and no prior stroke or TIA

N.B. Individual patient characteristics (eg, prior embolic stroke or perioperative stroke/TIA) may override suggested risk stratification
Suggested Risk Stratification: Venous Thromboembolism

**High Risk**
- Recent VTE (<3 months ago)
- Severe thrombophilia (e.g., antiphospholipid antibodies)

**Moderate Risk**
- VTE within the past 3-12 months
- Nonsevere thrombophilia (e.g., heterozygous factor V mutation)
- Recurrent VTE
- Active cancer (treated within 6 months or palliative)

**Low Risk**
- Prior VTE >12 months ago and no other risk factors
<table>
<thead>
<tr>
<th><strong>Inclusion criteria</strong></th>
<th><strong>Exclusion criteria</strong></th>
<th><strong>Before surgery</strong></th>
<th><strong>After surgery</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age &gt;18 years, needing to undergo therapy with low-molecular-weight heparin</td>
<td>- Allergy to unfractionated heparin or low-molecular-weight heparin</td>
<td>- If preoperative INR is 2-3, stop warfarin 5 days before surgery (ie, hold 4 doses)</td>
<td>- Restart low-molecular-weight heparin approximately 24 hours after procedure or consider thromboprophylactic dose of low-molecular-weight heparin on first postoperative day if patient is at high risk for bleeding</td>
</tr>
<tr>
<td>- Treating physician thinks patient needs bridging therapy (see Table 2)</td>
<td>- Weight &gt;150 kg</td>
<td>- If preoperative INR is 3-4.5, stop warfarin 6 days before surgery (ie, hold 5 doses)</td>
<td>- Discuss above with surgeon</td>
</tr>
<tr>
<td>- Medically and hemodynamically stable</td>
<td>- Pregnant woman with a mechanical valve</td>
<td>- Start low-molecular-weight heparin 36 hours after last warfarin dose, as follows:</td>
<td>Start warfarin at patient’s preoperative dose on postoperative day 1</td>
</tr>
<tr>
<td>- Scheduled for elective procedure or surgery</td>
<td>- History of bleeding disorder or intracranial hemorrhage</td>
<td>- Enoxaparin 1 mg/kg subcutaneously every 12 hours, or</td>
<td>Daily prothrombin time and INR until patient is discharged and periodically thereafter until INR is in the therapeutic range</td>
</tr>
<tr>
<td></td>
<td>- Creatinine clearance &lt;30 mL/min</td>
<td>- Enoxaparin 1.5 mg/kg subcutaneously every 12 hours, or</td>
<td>Daily phone follow-up with pharmacist to assess for adverse effects (eg, bleeding)</td>
</tr>
<tr>
<td></td>
<td>- Gastrointestinal bleeding within the last 10 days</td>
<td>- Dalteparin 120 U/kg subcutaneously every 12 hours, or</td>
<td>Complete blood cell count with platelets on day 3 and day 7</td>
</tr>
<tr>
<td></td>
<td>- Major trauma or stroke within the past 2 weeks</td>
<td>- Dalteparin 200 U/kg subcutaneously every 24 hours, or</td>
<td>Discontinue low-molecular-weight heparin when INR is 2-3 for 2 consecutive days</td>
</tr>
<tr>
<td></td>
<td>- History of heparin-induced thrombocytopenia or severe thrombocytopenia</td>
<td>- Tinzaparin 175 U/kg subcutaneously every 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Language barrier</td>
<td>- Give last dose of low-molecular-weight heparin approximately 24 hours before procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Potential for medication noncompliance</td>
<td>- Educate patient in self-injection and provide written instructions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Unsuitable home environment to support therapy</td>
<td>- Discuss plan with surgeon and anesthesiologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Severe liver disease</td>
<td>- Check INR the morning of surgery to ensure that INR is less than 1.5 or in some cases (eg, neurologic surgery) less than 1.2</td>
<td></td>
</tr>
</tbody>
</table>
Anticoagulant therapy

Preoperative timing of bridging — We generally initiate heparin bridging three days before a planned procedure (ie, two days after stopping warfarin), when the PT/INR has started to drop below the therapeutic range.

- **LMW heparin** – We discontinue LMW heparin 24 hours before the planned surgery or procedure, based on a biologic half-life of most subcutaneous LMW heparins of approximately three to five hours.

  If a twice-daily LMW heparin regimen is given, the evening dose the night before surgery is omitted, whereas if a once-daily regimen is given (eg, dalteparin 200 international units/kg), one-half of the total daily dose is given on the morning of the day before surgery. This ensures that no significant residual anticoagulant will be present at the time of surgery, based on studies that have shown a residual anticoagulant effect at 24 hours after stopping therapeutic-dose LMW heparin, and it is consistent with the 2012 ACCP Guidelines.
Anticoagulant therapy

Postoperative timing of bridging —

- The resumption of bridging, especially when given as a therapeutic-dose regimen, should be delayed until there is adequate hemostasis based on a clinical assessment of the wound site, drainage fluid amount, and expected postoperative bleeding; coupled, where appropriate, with hemoglobin levels. This assessment will vary depending on the surgery type and individual patient considerations, and it may be difficult for surgery where ongoing bleeding is not readily apparent (eg, cardiac, intracranial).

- For those undergoing major surgery or those with a high bleeding risk procedure, therapeutic-dose unfractionated heparin or LMW heparin should be delayed for 48 to 72 hours after hemostasis has been secured.

- For most minor procedures associated with a low bleeding risk in which bridging is used (eg, laparoscopic hernia repair), therapeutic-dose unfractionated heparin or LMW heparin can usually be resumed 24 hours after the procedure.

- Postoperatively, warfarin is generally resumed on the same postoperative day as the heparin. Heparin can be discontinued when the INR reaches the therapeutic range for individuals at moderate thromboembolism risk.
Anticoagulant therapy

Bridging dose regimens

Three dose regimens have been studied:

- A high-dose (therapeutic-dose)
- A low-dose (prophylactic-dose)
- An intermediate-dose regimen has recently been studied for bridging and is intermediate in anticoagulant intensity between high- and low-dose regimens.

Anticoagulant therapy

- **Therapeutic dosing** – Therapeutic dosing (also called "full dose") is appropriate for bridging anticoagulation for individuals with a potential arterial thromboembolic source (e.g., atrial fibrillation, mechanical heart valve) or VTE within the preceding month. Typical regimens include enoxaparin 1 mg/kg bid or 1.5 mg/kg daily, dalteparin 100 International Units/kg bid or 200 International Units/kg daily, tinzaparin 175 International Units/kg daily.

- **Intermediate dosing** – Intermediate dose anticoagulation may be appropriate for individuals with atrial fibrillation or VTE within the preceding month when bridging is needed but concerns about bleeding are greater. Typical regimens include enoxaparin 30 mg bid or 40 mg daily, dalteparin 5,000 International Units daily.

- **Prophylactic dosing** – Prophylactic dose anticoagulation (also called "low dose") generally is not used for bridging in patients with atrial fibrillation, because there is no evidence that prophylactic dose heparin prevents stroke in this setting. This dose level may be reasonable in patients who have had a VTE event between within the preceding 3 to 12 months. Typical prophylactic regimens include enoxaparin, 40 mg once daily, or dalteparin 5000 units subcutaneously once daily.

*Chest. 2012 Feb. 141(2 Suppl):e326S-50S*
## Anticoagulant therapy

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Prophylactic dose</th>
<th>Therapeutic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>5000 IU qd</td>
<td>100 IU/kg/12 h, 200 IU/kg/24 h</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg qd</td>
<td>1 mg/kg/12 h, 1.5 mg/kg/24 h</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>38 IU/kg qd</td>
<td>87 IU/kg/12 h</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4500 IU qd</td>
<td>175 IU/kg/24 h</td>
</tr>
</tbody>
</table>

Whom not to bridge: Dental, cataract, and colonoscopy patients
Patients undergoing a planned surgical intervention

The BRIDGE trial has now shown that also in VKA-treated patients, bridging with LMWH has no benefit regarding thromboembolism but is inferior concerning major bleeding.

Registry data have shown that bridging is still inappropriately used in NOAC patients, leading to a significantly higher peri-procedural bleeding rate (without lower thrombo-embolic rate).

*Europace (2015) 17, 1467–1507*
Anticoagulant therapy

- Dabigadran
- Rivaroxaban
- Abixaban
- Edoxaban

Non-vitamin K antagonist Oral AntiCoagulants (NOACs)

European Heart Journal (2014) 35, 2383–2431
Anticoagulant therapy

In patients treated with the non-VKA direct oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, or edoxaban all of which have a well-defined ‘on’ and ‘off’ action, ‘bridging’ to surgery is in most cases unnecessary, due to their short biological half-lives. An exception to this rule is the patient with high thrombo-embolic risk, whose surgical intervention is delayed for several days.
Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonists anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel\textsuperscript{1,8}, Peter Verhamme\textsuperscript{2}, Marco Alings\textsuperscript{3}, Matthias Antz\textsuperscript{4}, Hans-Christoph Diener\textsuperscript{5}, Werner Hacke\textsuperscript{6}, Jonas Oldgren\textsuperscript{7}, Peter Sinnaeve\textsuperscript{2}, A. John Camm\textsuperscript{8}, and Paulus Kirchhof\textsuperscript{9,10}

Advisors: Azhar Ahmad, M.D. (Boehringer Ingelheim Pharma), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim Pharma), Susanne Hess, M.D. (Bayer Healthcare Pharmaceuticals), Markus Müller, M.D., Ph.D. (Pfizer Pharma), Felix Münzel, Ph.D. (Daiichi-Sankyo Europe), Markus Schwertfeger, M.D. (Daiichi-Sankyo Europe), Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)
Patients undergoing a planned surgical intervention

*When to stop non-vitamin K antagonist anticoagulants?*

- **Patient characteristics**
  - kidney function,
  - age,
  - history of bleeding complications, and
  - concomitant medication

- **Surgical factors**
Patients undergoing a planned surgical intervention

Bridging with LMWH or heparin, as was proposed in AF patients with higher thrombo-embolic risk treated with VKAs, is not necessary in NOAC-treated patients since the predictable waning of the anticoagulation effect allows properly timed short-term cessation and reinitiation of NOAC therapy before and after surgery.

Europace (2015) 17, 1467–1507
Patients undergoing a planned surgical intervention or ablation

- Some procedures can be done without interruption of anticoagulation. Other procedures should be performed after temporary cessation of the NOAC.
- Schedule intervention at a time which is at least the interval after last intake as specified in the following table.
- For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 hours after the intervention.
- For complex procedures, one could administer a reduced venous thromboprophylactic or intermediate dose of LMWH 6 to 8 hours after surgery and restart NOACs 48–72 hours after the invasive procedure.
- Catheter ablation of AF is a special case. Continuous NOAC administration may be safe, although most centres will opt to drop the morning dose of NOAC or to give the last dose 12–24 hours before the planned ablation. Further controlled trial data are awaited.
### When to stop NOACs before a planned surgical intervention

**Last intake of drug before elective surgical intervention**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban, Edoxaban, Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>≥24 h</td>
<td>≥24 h</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td>≥48 h</td>
<td>≥48 h</td>
</tr>
<tr>
<td><strong>CrCl ≥80 ml/min</strong></td>
<td>≥24 h</td>
<td>≥24 h</td>
</tr>
<tr>
<td><strong>CrCl 50–80 ml/min</strong></td>
<td>≥36 h</td>
<td>≥24 h</td>
</tr>
<tr>
<td><strong>CrCl 30–50 ml/min §</strong></td>
<td>≥48 h</td>
<td>≥24 h</td>
</tr>
<tr>
<td><strong>CrCl 15–30 ml/min §</strong></td>
<td>not indicated</td>
<td>≥24 h</td>
</tr>
<tr>
<td><strong>CrCl &lt;15 ml/min</strong></td>
<td>no official indication for use</td>
<td>≥48 h</td>
</tr>
</tbody>
</table>

There is no need for bridging with LMWH/UFH

*Bold values deviate from common stopping rule of ≥24 h low risk and ≥48 h high risk.*

Low risk: low frequency and/or minor impact of bleeding. High risk: high risk or impact of bleeding. § many of these patients may be on the lower dose of dabigatran (i.e. 2 x 110 mg/d) or apixaban (i.e. 2 x 2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d) or edoxaban (30 mg/d).
## Classification of surgical interventions according to bleeding risk (part 1)

<table>
<thead>
<tr>
<th>Interventions not necessarily requiring discontinuation of anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental interventions</strong></td>
</tr>
<tr>
<td>- Extraction of one to three teeth</td>
</tr>
<tr>
<td>- Incision of abscess</td>
</tr>
<tr>
<td>- Paradental surgery</td>
</tr>
<tr>
<td>- Implant positioning</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
</tr>
<tr>
<td>- Cataract or glaucoma intervention</td>
</tr>
<tr>
<td><strong>Endoscopy without surgery</strong></td>
</tr>
<tr>
<td><strong>Superficial surgery</strong> (e.g. abscess incision, small dermatological excision)</td>
</tr>
<tr>
<td><strong>Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)</strong></td>
</tr>
<tr>
<td><strong>Endoscopy with biopsy</strong></td>
</tr>
<tr>
<td><strong>Prostate or bladder biopsy</strong></td>
</tr>
<tr>
<td><strong>Electrophysiological study or radiofrequency catheter ablation for right-sided supraventricular tachycardia</strong></td>
</tr>
<tr>
<td><strong>Non-coronary angiography</strong></td>
</tr>
<tr>
<td><strong>Pacemaker or ICD implantation</strong> (unless complex anatomical setting e.g. congenital heart disease)</td>
</tr>
</tbody>
</table>

[www.escardio.org/EHRA](http://www.escardio.org/EHRA)
In the case of procedures that carry a ‘risk for major bleeding’ (i.e. with a high frequency of bleeding and/or important clinical impact), it is recommended to take the last NOAC 48 h before. In patients with a CrCl of 15–30 mL/min, we recommend consideration of earlier interruption than 24 h for any of the FXa inhibitors, both for interventions with low and high risk for bleeding, i.e. last intake ≥36 h respectively ≥48 h before the procedure.

Procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture may require complete haemostatic function, and fall under the ‘high risk of bleeding’ category.
Patients undergoing an urgent surgical intervention

- Discontinue NOAC.
- Try to defer surgery at least 12 h and ideally 24 h after last dose.
- For patients on dabigatran: idarucizumab 5g IV reverses anticoagulation without pro-thrombotic side-effects and may allow urgent intervention.
- For patients on FXa inhibitors: no specific reversal agents available yet, but under development. A strategy with PCC or aPCC pre-operatively has not been studied and cannot be recommended.
- Coagulation tests can be considered (classical test or specific tests) but strategy based on these results has never been evaluated. Therefore such strategy cannot be recommended and should not be used routinely.
When to start non-vitamin K antagonist anticoagulants?

For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 h after the intervention. The same applies atraumatic spinal/epidural anaesthesia or clean lumbar puncture.

For many surgical interventions, however, resuming full dose anticoagulation within the first 48–72 h after the procedure may carry a bleeding risk that could outweigh the risk of cardio-embolism.

For procedures associated with immobilization, it is considered appropriate to initiate a reduced venous thromboprophylactic (e.g. 0.5 mg/kg/day of enoxaparin) or intermediate dose of LMWHs (e.g. 1 mg/kg/day of enoxaparin) 6–8 h after surgery if adequate haemostasis has been achieved, whereas full therapeutic anticoagulation by restarting NOACs is deferred 48–72 h after the invasive procedure.
Anticoagulant therapy

Press Release Archive: SPAF

Home → News → Press Releases → Press Release Archive: SPAF

26 November 2015

Praxbind® (idarucizumab) approved in European Union for the specific reversal of Pradaxa® (dabigatran etexilate)

- Idarucizumab is the first specific reversal agent for a NOAC to receive European approval¹
- Idarucizumab immediately reverses the anticoagulant effect of dabigatran²-⁴

Ingelheim, Germany, 26. November 2015 – The European Commission has approved Praxbind® (idarucizumab), a treatment to rapidly and specifically reverse the anticoagulant effects of Pradaxa® (dabigatran etexilate) in cases of emergency surgery/urgent procedures or in situations of life-threatening or uncontrolled bleeding.¹ Idarucizumab is the first specific reversal agent for a non-vitamin K antagonist oral anticoagulant (NOAC) to be approved in the European union.¹
NOACs Andidotes

Portola Announces Full Results From Positive Phase 3 ANNEXA-R study for Xarelto and Phase 3 ANNEXA-A study for Apixaban Demonstrating That Andexanet Alfa Rapidly and Significantly Reversed Anticoagulant Effect of Factor Xa Inhibitor XARELTO(R) AND Apixaban (A)

March 2, 2015 (GLOBE NEWSWIRE)
# Four NOACs to choose from

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran* 150/110 mg</th>
<th>Apixaban 5/2.5 mg</th>
<th>Rivaroxaban 20/15 mg</th>
<th>Edoxaban 60/30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>BID</td>
<td>BID</td>
<td>OD</td>
<td>OD</td>
</tr>
<tr>
<td><strong>RCTs: major bleeding vs warfarin&lt;sup&gt;1–4&lt;/sup&gt;</strong></td>
<td>15%</td>
<td>31%</td>
<td>Not significant</td>
<td>20%</td>
</tr>
<tr>
<td><strong>RCTs: stroke/SE vs warfarin&lt;sup&gt;1–4&lt;/sup&gt;</strong></td>
<td>26%</td>
<td>21%</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td><strong>Pivotal clinical trial validated by independent FDA analysis&lt;sup&gt;5&lt;/sup&gt;</strong></td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td><strong>Specific reversal agent available</strong></td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

# NOAC reversal agents will neutralize the activity of the drug

<table>
<thead>
<tr>
<th>NOAC reversal agent</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Dabigatran</td>
<td>Oral FXa inhibitors and heparins</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Humanized Fab: binds dabigatran with high affinity</td>
<td>Recombinant modified FXa: binds direct FXa inhibitors</td>
</tr>
<tr>
<td><strong>Phase III study</strong></td>
<td>RE-VERSE-AD™: patients requiring urgent surgery or with major bleeding</td>
<td>ANNEXA-4: patients with major bleeding</td>
</tr>
<tr>
<td><strong>Approval status</strong></td>
<td>Multiple countries</td>
<td>Not approved (in development)</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Widespread</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Idarucizumab does not reverse heparins and is easy to use

<table>
<thead>
<tr>
<th>Feature</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin interaction</td>
<td>No interaction</td>
<td>Reverses heparins</td>
</tr>
<tr>
<td>NOAC re-initiation</td>
<td>Dabigatran can be restarted after 24 hrs</td>
<td>Unknown for FXa inhibitors</td>
</tr>
<tr>
<td>Preparation</td>
<td>Ready to use</td>
<td>Requires reconstitution (~30–45 min)</td>
</tr>
<tr>
<td>Administration</td>
<td>IV bolus</td>
<td>Bolus followed by 2-hr infusion</td>
</tr>
<tr>
<td>Cost*</td>
<td>Similar to PCC</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Andexanet alfa is not approved in any country. *Cost comparison of PCC and idarucizumab may vary by country.
Idarucizumab is widely available including in >2500 hospitals in Europe and >2700 hospitals in the USA\(^1\)

Idarucizumab: available in Europe

Reversal agent for FXa inhibitors (andexanet alfa) in development: expected European availability late 2017/early 2018\(^2\)

2015  2016  2017  2018

*Andexanet alfa is not approved in any country.*

Idarucizumab was designed to specifically reverse the anticoagulant activity of dabigatran.

- Humanized Fab: binds free dabigatran and dabigatran bound to thrombin; no known off-target effects; does not reverse heparins or any other anticoagulants
- Binding affinity for dabigatran ~350x higher than dabigatran for thrombin
- No intrinsic procoagulant or anticoagulant activity
- IV administration, immediate onset of action
- Short half-life: Initial: ~45 min, Terminal: 4.5–8.1 hrs

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative continuation of beta-blockers is recommended in patients currently receiving this medication.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative initiation of beta-blockers may be considered in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status ≥3.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative initiation of beta-blockers may be considered in patients who have known IHD or myocardial ischaemia.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>When oral beta-blockade is initiated in patients who undergo non-cardiac surgery, the use of atenolol or bisoprolol as a first choice may be considered.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Initiation of peri-operative highdose beta-blockers without titration is not recommended.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Pre-operative initiation of beta-blockers is not recommended in patients scheduled for low-risk surgery.</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>
## Peri-operative statin use

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative continuation of statins is recommended, favouring statins with a long half-life or extended-release formulation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Pre-operative initiation of statin therapy should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

[European Heart Journal](https://www.escardio.org/guidelines)
Specific diseases

- Chronic heart failure
- Arterial hypertension
- Valvular heart disease
  - Aortic stenosis
  - Mitral stenosis
  - Aortic regurgitation and mitral regurgitation
  - Patients with prosthetic valve(s)
    - Prophylaxis of infective endocarditis
- Arrhythmias
  - Ventricular arrhythmias
  - Supraventricular arrhythmias
  - Bradyarrhythmias
  - Pacemaker/implantable cardioverter-defibrillator
- Renal disease
- Cerebrovascular disease
- Pulmonary disease

The use of unipolar electrocautery represents a significant risk to pacemaker-dependent patients. The electrical stimulus from electrocautery may inhibit demand pacemakers or may be transmitted to the generator as an inappropriate extrasystole. The electrocautery device may be the ground plate for the electrical circuit, such that the electrical current travels away from the generator. Keeping the electrocautery device away from the pacemaker, giving only brief, bursts and using the lowest possible amplitude may decrease the interference. In many studies, the authors recommended setting the pacemaker in an asynchronous or non-sensing mode in patients who are pacemaker dependent and whose underlying rhythm is unreliable, and interrogating the device after surgery to ensure appropriate programming and sensing pacing thresholds.

The implantable cardioverter defibrillator should be turned off during surgery and switched on in the recovery phase before discharge to the ward.

The indications for temporary pacemakers during the peri-operative period are generally the same as those for permanent pacemakers.

It is recommended that the hospital nominate a person who is responsible for programming of the implanted arrhythmia devices before and after surgery.

Patients with ICDs, whose devices have been pre-operatively deactivated, should be on continuous cardiac monitor throughout the period of deactivation. External defibrillation equipment should be readily available.

Patients who have asymptomatic bifascicular or trifascicular block are not recommended for routine management with a peri-operative temporary pacing wire.

European Heart Journal (2014) 35, 2383–2431