Common Questions and Answers on the Practical Use of Oral Anticoagulants in Non-Valvular Atrial Fibrillation

South West Medicines Information and Training and
Regional Drug and Therapeutics Centre (Newcastle)

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Oral anticoagulants (OACs) in AF - FAQs

Key factors influencing anticoagulant choice in Non-Valvular AF

- ***Licensing***: All novel OACS (NOACs) are licensed for prevention of stroke in non valvular atrial fibrillation plus at least one additional risk factor. Warfarin is licensed for use without additional risk factors present. http://www.medicines.org.uk/emc/
- ***NICE Guidance and patient choice:*** The decision about whether to start treatment with any anticoagulant in AF should be made after an informed discussion between the clinician and the patient about the risks and benefits of individual agents.
- ***Compliance***: NOACs are not a safe option in patients who are not suitable for warfarin for reasons of poor compliance or in those deemed to have too high a risk of bleeding for warfarin. Patients prescribed NOACS should have an on-going review of treatment, preferably after one month and then on a 3-monthly basis[1]
- ***Risk of haemorrhage:*** NOACs have been demonstrated to have a lower risk of catastrophic intracerebral haemorrhage but some (rivaroxaban and dabigatran 150mg) have a slightly higher risk of gastrointestinal haemorrhage.
- ***Reversal***: The major concern with the new anticoagulants is the lack of an effective antidote. This is counterbalanced to some degree by the lower risk of severe haemorrhage reported within clinical trials when compared to warfarin. NOACs however have a relatively short half-life compared to warfarin and protocols for managing bleeding events in NOAC treated patients are available.
- ***Acute bleeding:*** In the event of acute bleeding patients receiving a NOAC may require surgical haemostasis, fluid replacement or blood products. These may also be appropriate for those receiving warfarin in addition to vitamin K. Suggested approaches to the management of bleeding complications are outlined in the EHRA Practical guide on the use of NOACS[1]
- ***Renal function:*** Dose reduction (or cessation) of the newer drugs is required with reduced renal function
- ***Frequency of dosing:*** Dabigatran and apixaban require twice daily dosing, compared to once daily for rivaroxaban, edoxaban and warfarin.
- ***Extremes of BMI:*** The relative dose of NOACs may vary by 20-30% at extremes of bodyweight (<50 kg or >100-120 kg). This may be problematic given the difficulties in monitoring the therapeutic effects.
- ***Specific indications*** e.g. need for elective cardioversion, plans for ablation etc. Where continuation of anticoagulation therapy, up to and during the procedure, would be considered advantageous, the use of a NOAC could be appropriate where patient compliance can be reliably confirmed[1]. Warfarin may however be preferred given the possibility of reversal in the case of major bleeding.
- ***Monitored Dosage Systems:*** Neither warfarin nor dabigatran is suitable for use in a compliance aid.
- ***Comparative costs:*** Each of the newer drugs has a considerably higher acquisition cost than warfarin. When the cost of INR monitoring is taken into account, warfarin is likely to remain the least expensive option up-front. Comparative cost-effectiveness is not clear. If a NOAC is preferred and where all other factors are equal the NOAC with the lowest acquisition cost should be chosen
- ***Time in therapeutic range:*** The newer drugs are likely to be more beneficial in patients whose INR is regularly outside the therapeutic range despite good medication adherence.
- ***INR testing:*** INR testing with warfarin is time consuming, but provides an opportunity to monitor adherence and effectiveness.
- ***Experience:*** Compared to warfarin, there is less clinician experience of long term use of the NOACs.

Identifying patients taking anticoagulants

- Patients anticoagulated with either warfarin or newer agents should carry a card identifying their medication and who to contact in case of emergency related to their anticoagulation.

When might warfarin be the preferred option?

- In patients with a history of GI problems warfarin may be the preferred option as it has a more favourable GI side effect profile, and was associated with a lower rate of GI haemorrhage compared with rivaroxaban and dabigatran 150 mg. Compared with warfarin, apixaban does not significantly alter the risk of major GI bleeding. Warfarin has the additional advantage of being reversible.
- Patients co-administered medication that may inhibit metabolism and potentiate bleeding risk with novel agents (e.g. azole anti fungals, ritonavir) are probably safer managed on warfarin as the INR may be adjusted accordingly. Patients will still need appropriate dose adjustment of warfarin on commencement or withdrawal of such therapy.

Active swapping from warfarin to novel agents:

- Where patients are established on warfarin with a stable INR there is little or no reason to actively swap over to novel agents. Inadequate control of INR despite good compliance may be a reason to consider a NOAC, as are warfarin-specific side effects e.g. alopecia. There is a potential for inadequate anticoagulation during the transition between OACs.

The following tables address these common questions.

Oral anticoagulants (OACs) in AF - FAQs

	Warfarin[2]	Dabigatran[3]	Rivaroxaban[4]	Apixaban[5]	Edoxaban[6]
How do OACs do work?	Inhibits the production of vitamin K dependent clotting factors II, VII, IX and X.	Acts as a direct thrombin (factor IIa) inhibitor. It is formulated as dabigatran etexilate, a pro-drug converted to dabigatran after administration.	Acts as a selective direct factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.	Inhibits free and clot-bound factor Xa, and prothrombinase activity. Prevents thrombin generation and thrombus development. No direct effects on platelet aggregation, but indirectly inhibits aggregation induced by thrombin.	Inhibits free factor Xa, and prothrombinase activity. Reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus development.
What are their main contraindications?	• Known hypersensitivity to warfarin or any excipients • Haemorrhagic stroke • Clinically significant bleeding • Within 72 hours of major surgery with risk of severe bleeding • Within 48 hours postpartum • Pregnancy (first and third trimesters) • Drugs where interactions may lead to a significantly increased risk of bleeding	• Hypersensitivity to the active substance or any excipients. • Severe renal impairment (CrCL < 30 mL/min). • Active clinically significant bleeding. • Any lesion or condition considered a significant risk factor for bleeding. • Concomitant treatment with any other anticoagulant • Hepatic impairment or liver disease expected to have any impact on survival. • Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus, dronedarone. • Prosthetic heart valves requiring anticoagulant treatment.	• Hypersensitivity to the active substance or any excipients. • Active clinically significant bleeding. • Concomitant treatment with any other anticoagulant • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C • Pregnancy and breast feeding. • Prosthetic heart valves requiring anticoagulation treatment • Severe renal impairment (CrCL <15ml/min) • Dronaderone and other drug interactions	• Hypersensitivity to the active substance or any excipients. • Active clinically significant bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Any lesion or condition considered a significant risk factor for bleeding. • Concomitant treatment with any other anticoagulant • Prosthetic heart valves requiring anticoagulation treatment • Severe renal impairment (CrCL <15ml/min) • Dronaderone and other drug interactions	• Hypersensitivity to the active substance or any excipients. • Active clinically significant bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Any lesion or condition considered a significant risk factor for bleeding. • Uncontrolled severe hypertension • Concomitant treatment with any other anticoagulants • Prosthetic heart valves requiring anticoagulation treatment • Pregnancy and breast-feeding • End stage renal disease, or dialysis. • Active cancer
Lactose and wheat content.	Lactose Maize starch (Marevan®)	No lactose or wheat	Lactose No wheat	Lactose No wheat	No lactose Maize starch[7]

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When should individual OACs be avoided?	Intolerance to warfarin including allergy and rash. Demonstrated impossibility of monitoring arrangements Warfarin is teratogenic and should not be given in the first trimester of pregnancy	**AVOID** in patients with a history of poor medication adherence (unless poor adherence relates to e.g. difficulty managing flexible warfarin dosage that may be addressed through a fixed dose regime) The NOACs are **not** a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, drug overdose or trivial side effects related to warfarin. **Dabigatran is not stable in compliance aids such as blister packs.** Manufacturers advise to avoid use in pregnancy.			
What dose should be used? **(CrCl above 50 mL/min)**	For patients who require rapid anticoagulation the usual adult induction dose of warfarin is 5–10 mg on the first day (elderly patients should receive a lower induction dose). For patients who do not require rapid anticoagulation, a lower loading dose can be used over 3–4 weeks. In both cases subsequent doses depend upon the prothrombin time, reported as INR (international normalised ratio).	• Patients under 80 years: 150 mg twice daily • Patients >80 years: 110 mg twice daily (due to the increased risk of bleeding in this population) • Reduce to 110 mg twice daily in patients who are taking verapamil • Consider 110 mg twice daily when the thromboembolic risk is low and the bleeding risk is high (e.g. CrCL 30-50 mL/min) or patients weigh <50kg.	• 20 mg once daily with food	• 5 mg twice daily • Reduce to 2.5 mg twice daily in patients with two or more of the following characteristics: o Age ≥80 years o Body weight ≤60kg o Serum creatinine ≥1.5 mg/dL (133 micromoles/L)	• 60 mg once daily • Reduce to 30 mg once daily in patients with: o Body weight ≤60 kg o Concomitant P-gp inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole) • A trend towards decreasing efficacy with increasing creatinine clearance was observed compared to well-managed warfarin. • In the US, edoxaban is not licensed in patients with CrCL >95 mL/min, due to reduced efficacy.[8]
CrCl 30-49 mL/min	Renal insufficiency is a risk factor for bleeding. Consider apixaban in preference to warfarin with eGFR of 30–50 ml/min/1.73 m^2.[9]	110-150 mg twice daily	Reduce dose to 15 mg daily	Use normal dose	Reduce dose to 30 mg daily
CrCl 15-29 mL/min		Do not use		Reduce dose to 2.5 mg twice daily	
CrCl < 15mL/min		Do not use			
Safety	Long-term safety based on 50 years use in clinical practice.	No information available on long-term safety. Reduce dose in renal impairment (based on Cockcroft Gault calculation of CrCl)			

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What pre-treatment testing and ongoing monitoring is required?[10]	**Tests prior to starting treatment** Clotting screen, U&Es, LFTs, FBC, BP, CrCl, Thyroid status Ongoing monitoring requires adjustment to the individual needs of the patient and therefore requires regular monitoring using blood tests.	**Tests prior to starting treatment** Clotting screen, U&Es, LFTs, FBC, BP, CrCl **Monitoring until patient is stabilised** Ideally assess every 3 months to: • Assess compliance and reinforce advice regarding regular dosing schedule. • Enquire about adverse effects such as bleeding. • Assess for the presence of thromboembolic events • Enquire about other medicines, including OTC medicines. **Ongoing monitoring** U&Es, LFTs, FBC at least once a year especially in elderly and patients with renal impairment. Repeat U&Es every 6 months if CrCl 30–60 mL/min, patient > 75 years or fragile. Repeat U&Es every 3 months if CrCl 15–30 mL/min. More frequent U&Es /LFTs advised where intercurrent illness may impact on renal or hepatic function.	**Tests prior to starting treatment** Clotting screen, U&Es, LFTs, FBC, BP, CrCl **Monitoring until patient is stabilised** Ideally assess every 3 months to: • Assess compliance and reinforce advice regarding regular dosing schedule. • Enquire about adverse effects such as bleeding. • Assess for the presence of thromboembolic events • Enquire about other medicines, including OTC medicines. **Ongoing Monitoring** U&Es, LFTs, FBC at least once a year. Repeat U&Es every 6 months if CrCl 30–60 mL/min or every 3 months if CrCl 15–30 mL/min. More frequent U&Es /LFTs advised where intercurrent illness may impact on renal or hepatic function.		

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Does the risk of a bleed vary between OACs?	See respective agent for comparison	*Major bleeding*: No difference between dabigatran 150 mg BD and warfarin. Less common with dabigatran 110 mg BD than warfarin *GI bleeding*: More common with dabigatran 150 mg BD than warfarin (p=0.0008). No difference between dabigatran 110 mg BD and warfarin. *Intracranial bleeding*: Less common with both doses of dabigatran than with warfarin (p<0.001). Bleeding risk high in the frail and elderly, particularly with renal impairment and low body weight.	*Major bleeding*: No difference between rivaroxaban and warfarin. *GI bleeding*: More common with rivaroxaban than warfarin (p<0.001) *Intracranial bleeding*: less common with rivaroxaban than warfarin (p=0.02)	*Major bleeding*: Less common with apixaban than warfarin (p<0.001) *GI bleeding*: No difference between apixaban and warfarin *Intracranial bleeding*: Less common with apixaban than warfarin (p<0.001)	*Major bleeding* Less common with edoxaban than warfarin (p<0.001). *GI bleeding* More common with edoxaban than warfarin (p=0.03) *Intracranial bleeding* Less common with edoxaban than warfarin (p<0.001)
Can bleeding be reversed?	Vitamin K is an effective and well known antidote, readily available should a severe bleed occur whilst being treated	Patients with bleeding risk factors excluded from pivotal trial. Clearance can be increased with haemodialysis. Prolonged bleeding has increased morbidity and possibly contributed to deaths[13]. Reversal agent recently licensed and launched.[11] Quickly normalises clotting times in people with uncontrolled bleeding or requiring emergency surgery, but very limited evidence of clinical safety and efficacy.	Reversal agent in phase III trials[12]	Reversal agent in phase III trials[12]	Reversal agent in phase III trials[12]

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What are the half-lives of the OACs?	About 40 hours	GFR [mL/min]	half-life in hours (range)	5 to 9 hours in young individuals, 11 to 13 hours in the elderly.	12 hours	10 to 14 hours
		≥ 80	13.4 (11.0-21.6)			
		≥ 50 - < 80	15.3 (11.7-34.1)			
		≥ 30 - < 50	18.4 (13.3-23.0)			
		< 30	27.2 (21.6-35.0)			
What are the common side effects?	Nausea, vomiting, diarrhoea, jaundice, alopecia, rash, hepatic dysfunction, pyrexia.	Dyspepsia more frequent with both doses of dabigatran than warfarin. GI adverse events frequently led to drug discontinuation (7%, 6.5% and 3.9% in the dabigatran 150 mg, 110 mg and warfarin groups respectively). The rate of myocardial infarction (MI) was numerically, but not statistically significantly, higher with dabigatran in the pivotal trial (0.82% for 110 mg and 0.81% for 150 mg vs. 0.64% p=0.12).[13-15] Two meta-analyses showed that dabigatran was associated with a significantly higher risk of MI. The control groups varied and included enoxaparin, warfarin and placebo.[16,17]		There were no significant differences in the incidence of any adverse event other than bleeding in the pivotal rivaroxaban trial.[18] The rate of MI was numerically, but not statistically significantly lower, in the rivaroxaban arm compared with warfarin.	There were no significant differences between warfarin and apixaban in the incidence of any adverse events in the pivotal trial.[19]	There were no significant differences between warfarin and edoxaban in the incidence of any adverse events in the pivotal trial.[20]

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	Warfarin[2]	Dabigatran[3]	Rivaroxaban[4]	Apixaban[5]	Edoxaban[6]
How do you switch between anticoagulants? *There is a potential for inadequate anticoagulation during the transition between NOACs and warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternative anticoagulant.*	When converting patients from warfarin therapy to a NOAC, discontinue warfarin and start: • dabigatran when the INR is below 2.0 • rivaroxaban when INR is below 3.0 • apixaban when INR is below 2.0 • edoxaban when INR is ≤ 2.5 INR values may be falsely elevated after the intake of NOACs.	When converting from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows: For CrCl >50 mL/min, start warfarin 3 days before discontinuing dabigatran. For CrCl 31-50 mL/min, start warfarin 2 days before discontinuing dabigatran. For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing dabigatran For CrCl <15 mL/min, no recommendations can be made – consult with haematologist. Because dabigatran can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days.	When converting from rivaroxaban to warfarin, rivaroxaban should be continued until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing guided by INR testing. While patients are on both rivaroxaban and warfarin, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose	When converting from apixaban to warfarin, continue apixaban for at least 2 days after starting warfarin therapy. After 2 days of co-administration of apixaban and warfarin, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin until the INR is 2 or more	When converting from edoxaban to warfarin, continue edoxaban until the INR is ≥ 2.0. A loading dose of warfarin is **not** recommended. For patients currently on a 60 mg dose, administer edoxaban at a dose of 30 mg once daily together with an appropriate VKA dose. For patients currently on a 30 mg dose, administer edoxaban at a dose of 15 mg once daily together with an appropriate VKA dose. During the first 14 days of concomitant therapy measure the INR at least 3 times, just prior to the daily dose of edoxaban. Edoxaban can contribute to an elevated INR.
Converting from parenteral anticoagulants	The exact regimen depends on individual circumstances. Parenteral anticoagulants are generally continued until the INR is in the desired range.	Discontinue the parenteral anticoagulant and start dabigatran 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment.	For patients currently receiving a parenteral anticoagulant, rivaroxaban should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).	Switching treatment from parenteral anticoagulants apixaban (and vice versa) can be done at the next scheduled dose. These agents should not be administered simultaneously.	These agents should not be administered simultaneously. *Subcutaneous anticoagulants:* Discontinue the parenteral anticoagulant and start edoxaban at the time of the next scheduled dose. *Intravenous anticoagulants* Discontinue the infusion and start edoxaban 4 hours later.

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<table>
<tr><th></th><th>Warfarin[2]</th><th>Dabigatran[3]</th><th>Rivaroxaban[4]</th><th>Apixaban[5]</th><th>Edoxaban[6]</th></tr>
<tr><td rowspan="2">What are the main drug interactions?</td><td>Drug-food interactions
Cranberry juice and alcohol interact with warfarin. Some foods interact with warfarin (e.g. foods containing high amounts of Vitamin K).

Drug-drug interactions
Many interactions requiring additional INR monitoring.</td><td>Drug-food interactions
There are no known food interactions.

Drug-drug interactions
Contraindicated with the strong P-gp inhibitors ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone.
Use with caution if co-administered with mild to moderate P-gp inhibitors such as amiodarone, quinidine, verapamil, & ticagrelor.
Co-administration with P-gp inducers such as rifampicin, St John’s Wort, carbamazepine or phenytoin) should be avoided.
SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups.</td><td colspan="2">Drug-food interactions
There are no known food interactions.

Drug-drug interactions
Not recommended with concomitant systemic administration of strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole or HIV protease inhibitors.
Strong inducers of both CYP3A4 and P-gp (such as rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s Wort) should be co-administered with caution because of the risk of a loss of effectiveness.</td><td>Drug-food interactions
There are no known food interactions.

Drug-drug interactions
P-gp inhibitors: use with ciclosporin, dronedarone, erythromycin, or ketoconazole requires edoxaban dose reduction. No dose reduction required with quinidine, verapamil or amiodarone. Other P-gp inhibitors have not been studied.
P-gp inducers: use with caution.
Chronic use with NSAIDs not recommended.</td></tr>
<tr><td colspan="5">Concomitant administration with any other anticoagulants is contraindicated (some overlap may be necessary whilst transferring between anticoagulants).
Consult the SPCs for full details of interactions.</td></tr>
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OAC use with no clinically important bleeding risk	Dental procedures — outpatient dental surgery (including extractions) can usually be undertaken without temporarily stopping or reducing the dose of warfarin. It is recommended that the INR is checked 72 hours before dental surgery. The risk of significant bleeding in people with a stable INR within the range of 2 to 4 is very small, but the risk of thrombosis may be increased if oral anticoagulants are temporarily discontinued Surgery — in general, warfarin is usually stopped 5 days before planned surgery, and once the person's international normalised ratio (INR) is less than 1.5 surgery can go ahead. Warfarin is usually resumed at the normal dose on the evening of surgery or the next day if haemostasis is adequate.	The procedure can be performed just before the next dose of dabigatran, rivaroxaban or apixaban is due, or approximately 18–24 hours after the last dose was taken (treatment should be restarted 6 hours later). For dental procedures, consider prescribing tranexamic acid 5% mouth wash; instruct the person to use 10 mL as a mouth wash four times a day for 5 days.			
OAC use and undergoing surgery with a low bleeding risk[21]		Dabigatran should be stopped 24 hours before the procedure. If the person has creatinine clearance 50–80 mL/min dabigatran should be stopped 36 hours before the intervention If the person has creatinine clearance 30–50 mL/min dabigatran should be stopped 48 hours before the intervention	Rivaroxaban should be stopped 24 hours before the procedure. If the person has a creatinine clearance between 15–30 mL/min rivaroxaban should be stopped 36 hours before the procedure.	Apixaban should be stopped 24 hours before the procedure. If the person has a creatinine clearance between 15–30 mL/min, apixaban should be stopped 36 hours before the procedure.	Edoxaban should be stopped 24 hours before the procedure.
OAC use and undergoing surgery with a high bleeding risk[21]		Dabigatran should be stopped 48 hours before the procedure. If the person has creatinine clearance 50–80 mL/min dabigatran should be stopped 72 hours before the intervention If the person has creatinine clearance 30–50 mL/min dabigatran should be stopped 96 hours before the intervention	Rivaroxaban should be stopped 48 hours before the procedure.	Apixaban should be stopped 48 hours before the procedure.	
Restarting OACs after surgery	See local guidelines. Treatment should be restarted after the invasive procedure or surgical intervention as soon as possible **provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician**. Onset of action of NOACs is much faster than that of warfarin.				

NO CLINICALLY IMPORTANT BLEEDING RISK	SOME EXAMPLES OF SURGERY WITH LOW BLEEDING RISK	SOME EXAMPLES OF SURGERY WITH HIGH BLEEDING RISK
• DENTAL INTERVENTIONS SUCH AS; EXTRACTION OF 1 TO 3 TEETH, PERIODONTAL SURGERY, INCISION OF ABSCESS AND IMPLANT POSITIONING.CATARACT OR GLAUCOMA INTERVENTIONS. • ENDOSCOPY WITHOUT SURGERY. • MINOR SURGERY (E.G. ABSCESS INCISION AND SMALL DERMATOLOGIC EXCISIONS).	• ENDOSCOPY WITH BIOPSY. • PROSTATE OR BLADDER BIOPSY. • ELECTROPHYSIOLOGICAL STUDY OR RADIOFREQUENCY CATHETER ABLATION FOR SUPRAVENTRICULAR TACHYCARDIA (INCLUDING LEFT-SIDED ABLATION VIA SINGLE TRANS-SEPTAL PUNCTURE). • ANGIOGRAPHY. • PACEMAKER OR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) IMPLANTATION (UNLESS COMPLEX ANATOMICAL SETTING, E.G. CONGENITAL HEART DISEASE).	• COMPLEX LEFT-SIDED ABLATION (PULMONARY VEIN ISOLATION; VT ABLATION). • SPINAL OR EPIDURAL ANAESTHESIA. • LUMBAR DIAGNOSTIC PUNCTURE. • THORACIC SURGERY. • ABDOMINAL SURGERY. • MAJOR ORTHOPAEDIC SURGERY. • LIVER BIOPSY. • TRANSURETHRAL PROSTATE RESECTION. • KIDNEY BIOPSY.

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