INTRODUCTION

Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) is indicated for the prophylaxis and treatment of venous thrombosis and pulmonary embolism as well for the prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation (AF), cardiac valve replacement and myocardial infarction. Non-vitamin K antagonist oral anticoagulants (NOACs), which are safer alternatives to VKAs and do not require laboratory monitoring, are also available for many of these indications. AF is the most common scenario where chronic OAC is required for the prevention of stroke or systemic embolism, with a prevalence of about 3% in adults aged 20 years or older, and greater prevalence in elderly and patients with predisposing factors. In the European guidelines for the management of AF, OAC is recommended (class I) for all male AF patients with a CHA2DS2-VASc score (Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) score of 2 or more and all female AF patients with a CHA2DS2-VASc score of 3 or more, but should be also considered (class IIa) in male and female AF patients with CHA2DS2-VASc scores of 1 and 2, respectively. NOACs are regarded as first-line drug options for thromboembolic prevention in eligible patients with AF (eg, in preference to VKAs) but are not recommended for AF patients with mechanical heart valves and moderate-to-severe mitral stenosis.

The cornerstone of chronic antithrombotic prophylaxis in patients undergoing percutaneous coronary intervention (PCI), presenting with or without an acute coronary syndrome (ACS), is dual antiplatelet therapy (DAPT) with low-dose aspirin and a P2Y12 inhibitor. Coronary artery disease (CAD) coexists in 20%–30% of patients with AF, and approximately 5%–7% of PCI patients present with AF or other indications for chronic OAC. When indications for DAPT and OAC coexist, the optimal management of antithrombotic therapy becomes a clinical dilemma, because prescribing a triple antithrombotic therapy regimen is known to increase the chance of bleeding by four times compared with prescribing aspirin alone. Unfortunately, none of the two antithrombotic strategies (ie, anticoagulant and antiplatelet) can be easily discounted: OAC is superior to DAPT or single antiplatelet therapy for preventing cardioembolic events, but DAPT is superior to OAC for preventing stent thrombosis and recurrent coronary events. Indeed, stent thrombosis and coronary events are typically caused by platelet-rich thrombi that develop in the setting of high shear stress, while low shear stress thrombi develop in the left atrium of patients with AF, which is a less platelet-dependent process.

For years, the optimal management of triple antithrombotic therapy has been empirical, with expert consensus documents providing some sort of direction in a guideline-free zone. Patients on chronic OAC were generally excluded from landmark trials of antithrombopet therapy for ACS, but the use of antiplatelet agents was only partly restricted or left to the discretion of the treating physician in trials of NOACs for AF and represented the background therapy in ACS trials of NOACs. Subgroup analyses from these studies provide some indirect evidence on the risk–benefit balance of triple antithrombotic therapy in the era of NOACs. More recently, randomised controlled trials have been published that compare directly antithrombotic strategies for patients on OAC in need of antiplatelet therapy and seriously challenge the concept of full-dose triple antithrombotic therapy. A focused guideline update on DAPT has been issued in 2017 by the European Society of Cardiology that partly incorporates the new evidence and inform clinical practice. The scope of this review is to provide the reader with an update on the current status, evidence and recommendations regarding the field of antithrombotic therapy after PCI and/or ACS in patients on chronic OAC. The primary focus will be on patients with AF, because data for patients who may have other indications for OAC are extremely limited, and no dedicated randomised clinical studies are available.

TRIPLE OR DUAL ANTITHROMBOTIC THERAPY IN THE ERA OF VKAS

Two randomised trials explored antithrombotic strategies to improve the safety of triple antithrombotic therapy with warfarin and DAPT (ie, withdrawing aspirin or reducing the duration of triple therapy). The What is the Optimal antiplatelet &
Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial investigated the hypothesis that dual antithrombotic therapy with warfarin and clopidogrel (ie, without aspirin) reduces the risk of bleeding episodes within 1 year from PCI in comparison with a triple antithrombotic therapy regimen. The trial randomised in an open-label fashion 573 OAC patients (69% with AF, 65% treated with drug-eluting stents and 27.5% with ACS) and found a 64% relative decrease in bleeding episodes with dual antithrombotic therapy, driven by a reduced rate of minor bleeding episodes (table 1). There was no increase in the risk of thrombotic events with the lower intensity regimen, and all-cause mortality was significantly lower, but the study was underpowered for efficacy endpoints. Additional caveats of WOEST included the prolonged period of triple antithrombotic therapy in the control group, which does not reflect contemporary guideline recommendations (figure 1), and the relatively low proportion of patients with ACS, which makes the data less generalisable. Still, the WOEST trial was the first important piece of evidence that dropping aspirin achieves superior safety outcomes in candidates to triple antithrombotic therapy, leading to the initiation of multiple trials of aspirin-free strategies.

In the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial, 614 PCI patients treated with drug-eluting stents on OAC (one-third with ACS) were randomised to 6 weeks or 6 months of clopidogrel on top of aspirin and OAC use. The study can be considered as a trial of shorter versus longer DAPT duration in OAC patients, because clopidogrel was stopped earlier in the investigational group (figure 1). The primary endpoint, comprising a combination of ischaemic and bleeding events, did not differ at 9 months between the two groups, and no differences were also noted in secondary events (table 1). In a landmark analysis of events between 6 weeks and 6 months, the risk of bleeding was higher in the group on clopidogrel. Notably, the same power issues noted in WOEST, including the small proportion of ACS patients, also apply to the ISAR-TRIPLE study, challenging the interpretation. However, a consistent message from these studies, which is consistent with the findings from a nationwide registry, is the clinical need to minimise the duration of triple antithrombotic therapy as much as possible and take patient-by-patient decisions on using triple or dual antithrombotic therapy depending on the balance of the individual bleeding and ischaemic risks.

**Lessons from studies of NOACs for ACS**

In three phase II trials of patients with ACS, the addition of dabigatran, apixaban or rivaroxaban to DAPT was associated with a dose-dependent increase in bleeding events. The efficacy and safety of selected doses of apixaban and rivaroxaban were further investigated in two larger trials of patients with ACS. The Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE 2) study was terminated prematurely due to evidence of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in ischaemic events. Conversely, in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome (ATLAS-ACS-2) study, a very low-dose of rivaroxaban (2.5 mg twice daily) resulted in significantly less ischaemic events at the price of increased major and intracranial bleeding. In further scrutiny of a safer rivaroxaban-based strategy for patients with ACS, a phase II study recently reported the same risk of clinically significant bleeding with very low-dose rivaroxaban and a P2Y12 inhibitor (ie, without aspirin) compared with DAPT, but whether this strategy is also similarly effective remains uncertain. Rivaroxaban is currently indicated by the European Medical Agency for the prevention of atherothrombotic events in patients with ACS and elevated cardiac biomarkers and is given by clinical practice guidelines a class IIb recommendation for combination therapy with DAPT.
**Table 1** Randomised studies of dual or triple antithrombotic therapy in patients on chronic OAC in need of antiplatelet therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients (N)</th>
<th>ACS (%)</th>
<th>DES (%)</th>
<th>Intervention(s)*</th>
<th>Control*</th>
<th>Primary outcome</th>
<th>Follow-up</th>
<th>Key findings</th>
</tr>
</thead>
</table>
| WOEST             | 2013 | 573 patients receiving VKA and undergoing PCI with stenting | 27      | 64      | Clopidogrel 75 mg daily for 1–12 months | Aspirin 80–100 mg daily and clopidogrel 75 mg daily for 1–12 months | Any bleeding episode | 12 months | ► Bleeding episodes were observed in 19.4% of patients receiving DAT and 44.4% of patients receiving TAT (HR 0.36, 95% CI 0.26 to 0.50, p<0.0001).  
► The combined secondary endpoint of death, MI, stroke, target-vessel revascularization and stent thrombosis was observed in 11.1% of patients receiving DAT and 17.6% of patients receiving TAT (adjusted HR 0.56, 95% CI 0.35 to 0.91). |
| ISAR-TRIPLE       | 2015 | 614 patients receiving VKA and undergoing PCI with DES | 32      | 100     | Aspirin 75–200 mg daily and clopidogrel 75 mg daily for 6 weeks | Aspirin 75–200 mg daily and clopidogrel 75 mg daily for 6 months | Death, MI, definite stent thrombosis, stroke or TIMI major bleeding | 9 months | ► The primary endpoint was observed in 9.8% of patients receiving shorter TAT and 8.8% of patients receiving longer TAT (HR 1.14, 95% CI 0.68 to 1.91, p=0.63).  
► The combined secondary endpoint of cardiac death, MI, ischaemic stroke and definite stent thrombosis was observed in 4.0% of patients receiving shorter TAT and 4.3% of patients receiving longer TAT (HR 0.93, 95% CI 0.43 to 2.05).  
► The secondary safety endpoint of TIMI major bleeding was observed in 5.3% of patients receiving shorter TAT and 4.0% of patients receiving longer TAT (HR 1.13, 95% CI 0.64 to 2.04). |
| PIONEER-AF        | 2016 | 2124 patients with NVAF undergoing PCI with stenting | 52      | 68      | Rivaroxaban 10–15 mg once daily and clopidogrel 75 mg daily or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily for 12 months (group 1).  
► Rivaroxaban 2.5 mg twice daily (10–15 mg if clopidogrel discontinuation at 1 or 6 months), aspirin 75–100 mg once daily and clopidogrel 75 mg daily (or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily) for 1, 6 or 12 months. (group 2).  
► Rivaroxaban 2.5 mg twice daily plus clopidogrel 75 mg daily (or ticagrelor 90 mg twice daily or prasugrel 10 mg once daily) for 12 months (group 3). | VKA, aspirin 75–100 mg once daily and clopidogrel 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily) for 1, 6 or 12 months (group 3). | Clinically significant TIMI bleeding | 12 months | ► The primary endpoint was observed in 16.8% in group 1, 18.0% in group 2 and 20.7% in group 3 (HR for group 1 vs group 2: 0.59, 95% CI 0.47 to 0.76; HR for group 2 vs group 3: 0.63, 95% CI 0.50 to 0.80).  
► The combined secondary rates of death from cardiovascula causes, MI or stroke were similar in the three groups (6.5% in group 1, 5.6% in group 2 and 6.0% in group 3). |
| RE-DUAL PCI       | 2017 | 2725 patients with NVAF undergoing PCI with stenting | 51      | 83      | Dabigatran etexilate 110 mg twice daily plus clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily (110 mg DAT group).  
► Dabigatran etexilate 150 mg twice daily plus clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily (150 mg DAT group). | VKA, aspirin ≤100 mg once daily for 1–3 months and clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily (TAT group). | Major or clinically relevant non-major bleeding | 14 months (mean) | ► The primary endpoint was observed in (A) 15.4% of patients in the 110 mg DAT group and 26.9% of patients in the TAT group (HR 0.52, 95% CI 0.42 to 0.63); (B) 20.2% of patients in the 150 mg DAT group and 25.7% of patients in the TAT group, which did not include elderly patients outside the USA (HR 0.72, 95% CI 0.58 to 0.88).  
► The combined secondary endpoint of death, MI, stroke, systemic embolism and unplanned revascularisation was observed in 13.7% of patients receiving DAT (two dabigatran doses combined) and 13.4% of patients receiving TAT (HR 1.04, 95% CI 0.84 to 1.29). |

*Where not otherwise specified, the intended length of therapy corresponds to the latest follow-up.  
ACS, acute coronary syndromes; CI, confidence interval; DAT, dual antithrombotic therapy; DES, drug-eluting stents; HR, hazard ratio; ISAR-TRIPLE, Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; RE-DUAL PCI, Randomized Evaluation of Dual Antithromboc...
This recommendation cannot be generalised to ACS patients with AF because the dose of rivaroxaban approved for stroke prevention (20 mg once daily) is fourfold higher than the dose tested in the ATLAS-ACS-2 trial. Overall, the results of ACS studies of NOACs are poorly generalisable to patients with AF, but points again towards the bleeding risk associated with triple antithrombotic therapy.

**Lessons from dedicated studies of NOACs in patients with AF undergoing PCI: PIONEER-AF and RE-DUAL PCI**

The Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist; WOEST, What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing.

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**Figure 1** Treatment strategies in trials of dual or triple antithrombotic therapy. The x axis depicts drug durations in months for each strategy. AF, atrial fibrillation; ASA, acetylsalicylic acid; DAT, double antithrombotic therapy; ISAR TRIPLE, Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation; PCI, percutaneous coronary intervention; PIONEER AF, Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist; WOEST, What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing.
The Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial compared in 2725 patients with AF who had undergone PCI (half of them in the setting of an ACS) two regimens of dual antithrombotic therapy that included dabigatran and mostly clopidogrel (ticagrelor in 12%) versus a regimen of triple antithrombotic therapy with warfarin. In the triple antithrombotic therapy group, aspirin was discontinued after 1 month in patients who received a bare-metal stent (17%) and after 3 months in patients who received a drug-eluting stent (83%) (figure 1). At a mean of 14 months, the risk of the primary endpoint in the 110 mg dabigatran dual-therapy group (major or clinically relevant non-major bleeding) was non-inferior (and superior) to the risk observed in the triple antithrombotic therapy group (table 1). The 150 mg dabigatran dual therapy group also met the non-inferiority objective compared with the triple therapy group but did not show superiority. The risk of thromboembolic events was non-inferior in the two dual therapy groups combined as compared with the triple therapy group. Notably, the protocol was amended to enrol a smaller number of patients, with reflections on the power of the trial to examine efficacy according to dabigatran dose. However, other study findings were consistent with the hypothesis of a net clinical benefit of each of the two dual antithrombotic therapy regimens. Overall, the RE-DUAL PCI study validated the WOEST hypothesis (ie, less bleeding with dual therapy) with greater power. These results are even more important given the shorter length of triple antithrombotic therapy in the control arm of RE-DUAL PCI compared with WOEST.

Two more trials of NOACs in patients undergoing PCI are ongoing with apixaban and edoxaban, respectively (table 2). In the A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart (AUGUSTUS) trial, about 4600 patients will be randomised to apixaban 5 mg twice daily plus clopidogrel or warfarin plus clopidogrel. Interestingly, a 2×2 factorial plan is envisaged to investigate whether aspirin should also be part of these combinations. In the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI) trial, edoxaban 60 mg once daily will be tested against standard triple antithrombotic therapy in about 1500 patients. In both trials, the primary endpoint will be a combined safety endpoint.

### RECOMMENDATIONS ON THE MANAGEMENT OF PATIENTS ON OAC UNDERGOING PCI WITH OR WITHOUT AN ACS

The focused update on DAPT from the European Society of Cardiology is so far the most updated document providing clinicians with recommendations on antiplatelet therapy duration in PCI patients with indication for OAC, but it does not include the results of RE-DUAL PCI, which were released after the guidelines were published. The document emphasises the need for implementing strategies to minimise PCI-related complications including (1) risk stratification for ischaemic and bleeding with a focus on modifiable risk factors, (2) keeping triple antithrombotic therapy to the shortest possible duration with dual antithrombotic therapy as an alternative, (3) using NOACs whenever possible instead of VKAs, at the lowest approved dose effective for stroke prevention.

### Table 2: Ongoing trials of NOACs in patients undergoing percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Study type</th>
<th>AUGUSTUS</th>
<th>ENTRUST-AF PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational drug(s)</td>
<td>Open label (apixaban vs warfarin) and blinded (aspirin vs placebo), randomised, factorial design</td>
<td>Open label, randomised</td>
</tr>
<tr>
<td>Clinicaltrials.gov identifier</td>
<td>NCT02415400</td>
<td>NCT02866175</td>
</tr>
<tr>
<td>Patients</td>
<td>~4600 patients with atrial fibrillation, and ACS or PCI or both</td>
<td>~1500 patients with atrial fibrillation that undergo a PCI with stenting</td>
</tr>
<tr>
<td>Experimental arm(s)</td>
<td>Apixaban 5 mg twice daily (or reduced dose of 2.5 mg twice daily) plus clopidogrel 2×2 factorial plan for aspirin.</td>
<td>Edoxaban 60 mg od (or reduced dose of 30 mg od)</td>
</tr>
<tr>
<td>Control arm</td>
<td>Warfarin plus clopidogrel 75 mg</td>
<td>Warfarin plus clopidogrel 75 mg od or prasugrel 10 mg od or ticagrelor 90 mg twice daily plus aspirin ≤100 mg od</td>
</tr>
<tr>
<td>Primary safety endpoint</td>
<td>International Society of Thrombosis and Haemostasis Major or clinical relevant non-major bleeding event</td>
<td>International Society of Thrombosis and Haemostasis Major or clinical relevant non-major bleeding event</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>Death, MI, stroke or stent thrombosis</td>
<td>Cardiovascular death, stroke, systemic embolism, MI or stent thrombosis</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6 months</td>
<td>12 months</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; AUGUSTUS, A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; ENTRUST-AF PCI, Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; MI, myocardial infarction; NOACs, non-vitamin K antagonist oral anticoagulants; od, once daily; PCI, percutaneous coronary intervention.

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tested in AF trials when combined with antiplatelet drugs, (4) considering an INR in the lowest part of the therapeutic range in case of VKAs use and (5) using proton pump inhibitors routinely.

In patients where concerns about the risk of ischaemic complications prevail, 1 month of triple antithrombotic therapy with OAC, aspirin and clopidogrel is recommended irrespective of the type of stent used but may be considered up to 6 months in patients at high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the risk of bleeding. When the period of triple antithrombotic therapy is concluded, a dual antithrombotic regimen with OAC and aspirin or clopidogrel is recommended up to 12 months, followed by OAC alone. The safety of using OAC alone after 12 months is supported by large registries, but dual antithrombotic therapy can still be considered beyond that timeframe in selected patients at very high risk of thrombotic events. In patients where concerns about the risk of bleeding complications prevail, triple antithrombotic therapy should not be prolonged beyond 1 month and can be even avoided using dual antithrombotic therapy with OAC and clopidogrel as an alternative. All the above recommendations are now class IIa with varying levels of evidence. When rivaroxaban is used in combination with aspirin and/or clopidogrel, the 15 mg once daily dose of rivaroxaban may be used instead of the conventional 20 mg once daily dose (class IIb), based on the design and results of the PIONEER-AF study. The regimens of dabigatran 110 mg and 150 mg investigated in the RE-DUAL PCI study can be easily implemented in clinical practice by addition of clopidogrel to OAC for 12 months. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy (class III) as the consequence of the low use in randomised clinical trials (ie, only 6% in PIONEER-AF) and the worrying signals of unacceptable bleeding risk in a small registry. Based on the above and the results of recent trials, figures 2 and 3 provide practical algorithms for the management of combination therapy with NOACs and antiplatelet drugs in two increasingly common scenarios: patients with AF undergoing PCI (presenting with or without ACS) and patients with ACS/PCI who develop newly onset AF. Case-by-case decisions are necessary for
patients with new or recent ACS/PCI who are on OAC due to causes other than AF (ie, recurrent thromboembolic events and mechanical prostheses). Finally, it should be considered that selected patients with AF at an unacceptably high bleeding risk with triple or dual antithrombotic therapy may benefit from a third option for stroke prevention that is left atrial appendage closure.

**SUMMARY/CONCLUSIONS**

Combination of anticoagulant and antiplatelet drugs increases the risk of bleeding but is requested by relatively common clinical scenarios in daily practice. A term of triple antithrombotic therapy is recommended for patients with AF presenting with PCI and/or ACS, but there is consensus that this should be as short as possible and that it should be avoided in patients where the concern of bleeding prevails over the concern of ischaemic complications. The introduction of NOACs and their clinical testing in the PCI setting may encourage the shift towards safer dual antithrombotic therapy strategies. Whether these ‘less-is-more’ combinations are also effective remains a matter of uncertainty due to the small size of the available studies and will likely be the objective of future study-level meta-analyses of the RE-DUAL PCI, PIONEER AF, AUGUSTUS and ENTRUST-AF PCI trials. Incorporation of ticagrelor and prasugrel into these schemes is challenging in a field where data are limited. Ultimately, patient-by-patient decision after characterisation of the individual ‘bleeding and ischaemic risk profile’ is the best strategy to achieve a net benefit in efficacy and safety.

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Author note  References that include an asterisk (*) are considered to be key references.

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REFERENCES


