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Cardiac Society of Nepal Consensus Recommendations for INR Monitoring and Warfarin Management

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Abstract

Background: Vitamin K antagonists (VKAs), particularly warfarin, remain the cornerstone of oral anticoagulation therapy in Nepal due to the high burden of rheumatic heart disease. Effective anticoagulation with VKAs requires meticulous monitoring of prothrombin time and international normalized ratio (PT/INR). However, significant variability exists in INR monitoring frequency, dose adjustment practices, laboratory standardization, and perioperative management across Nepal.

Objective: To develop standardized, practical, and Nepal-specific consensus recommendations for PT/INR monitoring and warfarin management using a structured modified Delphi process.

Methods: A three-round modified Delphi methodology was conducted among a multidisciplinary panel of clinicians involved in anticoagulation management in Nepal. Round 1 collected open-ended qualitative inputs to identify key thematic areas. In Round 2, structured consensus statements were developed and rated on a Likert scale. Statements with incomplete agreement were refined and re-evaluated in Round 3. Consensus thresholds were predefined, and recommendations were categorized accordingly.

Results: Following three rounds of the modified Delphi process, 15 consensus recommendations were endorsed. Strong consensus was reached on recommendations related to therapeutic INR targets, dose-adjustment strategies, INR re-testing intervals, drug-drug interactions, perioperative management, and monitoring strategies for unstable patients. Consensus was not reached for select recommendations concerning routine reversal strategies in asymptomatic supratherapeutic INR and prolonged INR monitoring intervals. Final consensus recommendations addressed INR monitoring, warfarin management, and context-specific strategies for resource-limited and rural settings.

Conclusion: This consensus provides a practical framework for PT/INR monitoring and warfarin management tailored to Nepal's healthcare context. Adoption of these recommendations may help standardize practice, reduce preventable complications, and guide future research and policy development.

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Introduction

Background

Vitamin K antagonists (VKAs), particularly warfarin, continue to be widely prescribed in Nepal for indications such as mechanical heart valves, rheumatic valvular heart disease, atrial fibrillation, venous thromboembolism, and selected hypercoagulable states.[1] Despite the growing availability of direct oral anticoagulants globally, VKAs remain in widespread use in Nepal owing to their affordability, availability, and established role in patients with mechanical prosthetic valves.[2]

However, VKAs possess a narrow therapeutic index and exhibit substantial inter- and intra-individual variability influenced by diet, drug interactions, comorbidities, genetic factors, and adherence. Suboptimal PT/INR monitoring and inappropriate dose adjustments are associated with significant risks of bleeding and thromboembolic complications, many of which are potentially preventable.[3]

Rationale: Why a Nepal-Specific PT/INR Consensus Is Needed

Population and Disease Profile

Nepal bears a disproportionately high burden of rheumatic heart disease, resulting in a large population of young and middle-aged patients requiring lifelong anticoagulation following mechanical valve replacement. Availability of medications and therapeutic products used for anticoagulation reversal and coagulopathy management remains limited. Similarly, many INR labs are poorly standardized, and many patients live in remote geographic areas.

Resource Constraints and Infrastructure

Access to standardized INR testing laboratories is uneven across Nepal. Inter-laboratory variability, delayed reporting, limited quality control, and inconsistent availability of point-of-care

INR testing devices complicate routine monitoring, particularly in rural and remote regions.

Health System and Economic Factors

Nepal's healthcare system is predominantly rural, with significant out-of-pocket expenditure. Travel distance, cost, and loss of wages often delay INR testing and follow-up, influencing real-world adherence to international guidelines that assume frequent monitoring and easy access to laboratory services.

Evidence Gaps

Most international guidelines on warfarin management are derived from high-income settings with robust infrastructure and do not adequately address challenges encountered in low- and middle-income countries. There is a paucity of Nepal-specific data to validate global recommendations.

Therefore, locally adapted, feasible, and resource-informed consensus recommendations are required to harmonize PT/INR monitoring and warfarin management practices in Nepal.

Objective

To provide standardized, Nepal-specific consensus recommendations on PT/INR monitoring and warfarin management using a structured modified Delphi methodology.

Scope

Included:

1. Indications for PT/INR testing
2. Target INR ranges
3. INR monitoring frequency
4. Warfarin dose adjustment strategies
5. Drug-drug interactions
6. Perioperative management
7. Considerations for rural and resource-limited settings

Out of Scope:

1. Pediatric anticoagulation
2. Detailed management of acute bleeding
3. Pharmacology of direct oral anticoagulants

Methodology

Study Design

This study employed a three-round modified Delphi consensus methodology to develop Nepal-specific recommendations for PT/INR monitoring and warfarin management. The Delphi technique was selected to systematically obtain expert agreement on complex clinical practices where high-quality local evidence is limited.

Expert Panel Selection

A task force consisting of writing committee members was formed by the Cardiac Society of Nepal (CSN) Executive Committee which included a multidisciplinary expert panel comprising cardiologists, cardiothoracic surgeons, internists, hematologists, pathologists and anesthesiologists with a minimum of five years of experience in anticoagulation management. Experts were selected based on clinical experience, academic involvement, and familiarity with warfarin management in Nepalese practice settings.

All invited participants provided informed consent prior to participation. Conflicts of interest were declared at enrollment and reconfirmed at each Delphi round.

Data Analysis

Only descriptive statistics were used. A percentage agreement for each statement was calculated. No inferential statistical analyses were performed, as the objective was consensus generation rather than hypothesis testing.

Ethical Considerations

This study involved expert opinion only and did not include patient data; therefore, formal ethical approval was not required.

Reporting Standard

The study is reported in accordance with established CREDES (Conducting and Reporting Delphi Studies) consensus reporting recommendations to ensure methodological transparency.

Consensus Process

A three-round modified Delphi process was conducted to achieve expert consensus. The process emphasized transparency, iterative refinement, and feasibility within the Nepalese healthcare context.

Delphi Rounds

Round 1: Exploration

Participants responded to open-ended questions regarding current practices, challenges, and gaps in PT/INR monitoring and warfarin management in Nepal. Qualitative responses were analyzed by the steering committee to identify key domains.

Round 2: Statement Development and Rating

Based on Round 1 themes, structured consensus statements were developed. Participants rated each statement using a three-point Likert scale (Agree/Neutral/Disagree) to simplify decision-making and reduce respondent burden.

Round 3: Refinement and Re-rating

Statements that did not achieve predefined consensus in Round 2 were revised for clarity, feasibility, and contextual relevance, and were re-rated in Round 3.

Consensus Definition

Consensus thresholds were defined a priori as follows:

1. Strongly Recommended: ≥70% agreement
2. Recommended: 60–69% agreement
3. No Consensus: <60% agreement

Percent agreement was calculated using the total number of respondents for each round. Neutral responses were included in the denominator. These thresholds were selected based on commonly adopted criteria in published Delphi consensus studies, where ≥70% agreement is frequently used to define consensus.

Results

A total of 53 structured statements across multiple thematic domains were generated from themes identified during Round 1 and disseminated in Round 2 for expert rating. Sixteen statements that did not achieve predefined consensus thresholds were revised and carried forward to Round 3. Following iterative refinement, 15 statements reached consensus and formed the final recommendations.

Consensus Recommendations

INR Monitoring and Warfarin Dose Adjustment

Strongly Recommended

1. In patients with INR 1.5-1.7 and a previously therapeutic INR, the total weekly warfarin dose should be increased by 5-10%, and INR should be rechecked after 7 days.
2. In patients with INR 3.5-4.0 without bleeding, the total weekly warfarin dose should be reduced by 10-15%, and INR should be rechecked after 7 days.
3. In patients with unstable INR values, INR testing should be performed at 7-day intervals until stability is achieved.

Recommended

In patients with INR 1.8-1.9 and stable prior to therapeutic values, immediate dose adjustment is not mandatory; INR should be repeated after 7-10 days.

Management of Supratherapeutic INR

Recommended

1. In patients with INR 4.0-6.0 without active bleeding, temporary withholding of 1-2 warfarin doses and/or reduction of the total weekly warfarin dose by approximately 5-15% may be considered, with repeat INR testing within 24-72 hours.
2. In patients with INR 6.0-9.0 without active bleeding, temporary discontinuation of warfarin with close INR monitoring is recommended. The decision to administer low-dose vitamin K should be individualized based on bleeding risk, urgency of reversal, and patient-specific clinical factors.

Strongly Recommended

In warfarin-treated patients with INR >9.0 requiring emergency surgery or with life-threatening conditions, rapid INR reversal using Prothrombin Complex Concentrate (PCC) and intravenous vitamin K is recommended. Fresh frozen plasma (FFP) may be used if PCC is unavailable. When FFP is used, ABO compatibility, patient volume status, and the risk of transfusion-associated circulatory overload should be considered, particularly in patients with valvular heart disease.

Areas Without Consensus (Evidence or Agreement Still Evolving)

1. Routine transfusion of FFP or PCC for asymptomatic supratherapeutic INR without bleeding
2. Universal pre-emptive reversal strategies in clinically stable patients
3. Extension of INR monitoring intervals beyond 6 weeks

These statements failed to reach consensus and are therefore not recommended.

Drug Interactions

Strongly Recommended

1. When enzyme-inhibiting drugs (e.g., amiodarone, metronidazole, fluconazole, erythromycin, ciprofloxacin) are initiated, INR should be checked within 2-3 days and warfarin dose adjusted according to INR response.
2. When enzyme-inducing drugs (e.g., rifampicin, carbamazepine, phenytoin) are initiated, INR should be checked within 3-5 days and warfarin dose adjusted accordingly.
3. When medications that increase bleeding risk without affecting INR (e.g., NSAIDs, aspirin, clopidogrel) are initiated, patients should be closely monitored for bleeding, and warfarin dose adjustment should be individualized.

Perioperative Management

Strongly Recommended

1. Warfarin should be discontinued 5-6 days prior to major surgery with a target INR <1.5.
2. In patients with mechanical heart valves undergoing emergency surgery for life-threatening conditions, rapid reversal with PCC and intravenous vitamin K is recommended; FFP may be used if PCC is unavailable.

Recommended

1. In patients with low-risk mechanical aortic valves without additional thromboembolic risk factors, omission of bridging anticoagulation may be considered on an individual basis.
2. For minor procedures with very low bleeding risk (e.g., dental procedures, cataract surgery), warfarin discontinuation is generally not required if INR is within the lower therapeutic range.

Resource-Limited and Rural Settings

Recommended

1. Use of point-of-care INR testing in settings with limited laboratory access, with telemedicine support for interpretation, dose adjustment, and follow-up.
2. Cautious extension of INR monitoring intervals may be considered in stable patients, particularly in rural or remote settings.

Decision-Making Algorithm

1. Assess indication and target INR
2. Review recent INR trends and stability
3. Adjust warfarin dose per consensus recommendations
4. Determine INR recheck interval
5. Consider patient-specific factors and resource availability

Discussion

Our consensus recommendations for PT/INR monitoring and warfarin management integrate international evidence with Nepal-specific contextual considerations. Warfarin therapy requires rigorous INR monitoring because of its narrow therapeutic index and delayed pharmacodynamic response, which is influenced by genetic, dietary, drug, and clinical factors.[3,4] The International Normalized Ratio standardizes prothrombin time across laboratories, facilitating safer long-term anticoagulation management. Therapeutic INR ranges vary by indication, with INR targets of 2.0-3.0 for most conditions and 2.5-3.5 for higher risk mechanical valves, consistent with established guidelines from hematology and anticoagulation societies.[5,6] Similarly, ACC and ESC guidance supports more frequent INR reassessment when values are unstable or when interacting medications are introduced.[7,8]

INR Monitoring Frequency and Stability

Evidence and international guideline frameworks support intensive INR monitoring when warfarin therapy is initiated, and monitoring intervals may be progressively extended once INR stability is achieved. Early monitoring (often 2-4 times per week) during initiation or after a dose change allows identification of trend direction and risks of overshoot or under anticoagulation. After stability is achieved (defined by consecutive therapeutic INR readings), monitoring intervals may progressively be extended to weekly, biweekly, and eventually monthly assessments in stable patients. Some guidelines allow INR monitoring intervals up to 8-12 weeks in very stable patients; however, this is based on populations with highly structured anticoagulation clinics and reliable follow-up systems.[9,10]

In Nepal's context, where access barriers and resource limitations are common, our recommendations balance safety with feasibility, emphasizing more frequent rechecking when INR is unstable, outside the therapeutic range, or after interacting drugs are introduced. These strategies align with established external warfarin management protocols that recommend INR measurement within 1-2 weeks for minor deviations and within 3-5 days when medications with strong interactions are initiated. [11,12]

Dose Adjustment Principles

Dose adjustments in warfarin therapy are typically small and incremental, usually 5-20% of the total weekly dose, to avoid overcorrection given the slow onset of effect. This approach is supported by clinical pharmacology literature and therapeutic guidelines, which emphasize dose changes based on trending INR values rather than a thsingle isolated result when possible.[5,13]

Our consensus reflects this principle by recommending incremental adjustments (5-10% or 10-15%) for mild subtherapeutic or supratherapeutic INR values with reassessment windows that respect warfarin's delayed steady state effect. These intervals also parallel guideline based recommendations that dose changes should not be made more frequently than every 5-7 days because of the half lives of clotting factors and delayed INR response.[3,14-16]

Management of asymptomatic supratherapeutic INR remains an area of evolving practice. The panel favored conservative management strategies for INR values between 4.0 and 9.0 in the absence of bleeding, emphasizing temporary dose withholding, cautious dose reduction, and closer INR surveillance rather than routine reversal interventions. This reflects concerns regarding overtreatment, limited access to reversal agents, and variability in monitoring resources within Nepal.

Drug Interactions and Perioperative Management

Warfarin's tendency for clinically important drug interactions with enzyme inhibitors and inducers (e.g., antibiotics, antifungals, anticonvulsants) is well documented. Our recommendation to check INR within 2-3 days after starting inhibitors and 3-5 days with inducers is consistent with established monitoring recommendations that advocate for closer monitoring when interacting medications are added or withdrawn.[9,16-19]

Perioperative management of warfarin is another area where global guidance supports tailored approaches based on thrombotic and bleeding risks. Elective major surgery typically requires warfarin cessation several days beforehand to allow INR reduction, while bridging protocols depend on individual thromboembolic risk profiles. This approach aligns with ACC and ESC guidance, which emphasize individualized perioperative anticoagulation strategies based on thromboembolic and bleeding risks rather than uniform bridging for all patients.[7,8] Though exact timing may vary by guideline and setting, the fundamental principle of stopping warfarin ahead of major surgery and individualizing bridging strategies is shared across international recommendations.[20,21]

Resource Limited and Rural Settings

A key Nepal-Specific strength of this consensus is the explicit inclusion of context sensitive strategies for resource limited and rural environments, such as the judicious use of point of care INR testing, and telemedicine supported decision making. These adaptations are essential in settings where conventional laboratory access is limited or delayed, and they echo broader calls in the literature to adapt INR monitoring schedules to local care realities while ensuring safety.[22]

Limitations and Challenges

1. Limited Nepal-specific outcome data
2. Small expert panel size
3. Variability in laboratory quality and availability
4. Lack of patient-reported perspectives, since there is absence of patient/public involvement
5. No formal implementation or audit strategy

Consensus was more difficult to achieve for management of asymptomatic supratherapeutic INR, reflecting variability in clinician preference, resource availability, and limited local evidence.

Conclusion

This consensus provides a practical, resource-sensitive framework for PT/INR monitoring and warfarin management in Nepal. By aligning global evidence with local realities, these recommendations aim to standardize care, reduce preventable complications, and support safer anticoagulation practices nationwide.

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Conflict of Interest and Editorial Independence Statement:

The corresponding author currently serves as Editor-in-Chief of the Nepalese Heart Journal. This consensus initiative was conceptualized and initiated before her editorial appointment. The project coordinator and expert panel were selected by the Cardiac Society of Nepal Executive Committee, independent of the journal. The author was not involved in the editorial handling, peer review, or final decision-making process for this manuscript, which was managed independently to ensure impartiality.

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Table 1. Evolution of Statements Through the Delphi Consensus Process

Delphi Round	Statements Disseminated	Revised / Merged	Carried Forward
Round 1 (Open-ended exploration)	Open-ended questions across major thematic domains	Responses synthesized into draft themes	Key themes identified
Round 2 (Structured rating)	53 structured statements	16 statements revised and refined	Partially agreed statements
Round 3 (Refinement and re-rating)	16 revised statements	Statements reworded for clarity and feasibility	Final consensus statements
Final	15 consensus recommendations endorsed	–	Endorsed recommendations

Table 2. Final Consensus Recommendations

Section	Recommendation	Consensus Category	% Agreement
Drug Interaction	Monitor for bleeding with NSAIDs/aspirin/clopidogrel	Strongly Recommended	100%
Perioperative	Stop warfarin 5-6 days before major surgery; target INR <1.5	Strongly Recommended	77.8%
Perioperative	Emergency surgery, PCC + IV vitamin K	Strongly Recommended	88.9%
Perioperative	Low-risk mechanical AVR: omission of bridging may be considered	Recommended	66.7%
Perioperative	Minor procedures usually do not require warfarin discontinuation	Recommended	83.3%
Resource-limited settings	Point-of-care INR testing with telemedicine support	Recommended	Consensus-derived
Resource-limited settings	Cautious extension of monitoring intervals in stable rural patients	Recommended	Consensus-derived