**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** NQF 0555

**Measure Title**: INR Monitoring for Individuals on Warfarin

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Not applicable

**Date of Submission**: 10/29/2018

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| **Instructions**  *Complete 1a.1 and 1a.12 for all measures.*  *Complete* ***EITHER 1a.2, 1a.3 or 1a.4*** *as applicable for the type of measure and evidence.*  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Standing Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Outcome: **3** Empirical data demonstrate a relationship between the outcome and at least one healthcare structure, process, intervention, or service. If not available, wide variation in performance can be used as evidence, assuming the data are from a robust number of providers and results are not subject to systematic bias. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence **4** that the measured intermediate clinical outcome leads to a desired health outcome. * Process: **5** a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence **4** that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence **4**  that the measured structure leads to a desired health outcome. * Efficiency: **6** evidence not required for the resource use component. * For measures derived from patient reports, evidence should demonstrate that the target population values the measured outcome, process, or structure and finds it meaningful. * Process measures incorporating Appropriate Use Criteria: See NQF’s guidance for evidence for measures, in general; guidance for measures specifically based on clinical practice guidelines apply as well.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors.* (*A PRO-based performance measure is not a survey instrument. Data may be collected using a survey instrument to construct a PRO measure.)*

Intermediate clinical outcome (*e.g., lab value*): Click here to name the intermediate outcome

Process: INR Monitoring for Individuals on Warfarin

Appropriate use measure: Click here to name what is being measured

Structure: Click here to name the structure

Composite: Click here to name what is being measured

**1a.2** **LOGIC MODEL** Diagram or briefly describe the steps between the healthcare structures and processes (e.g., interventions, or services) and the patient’s health outcome(s). The relationships in the diagram should be easily understood by general, non-technical audiences. Indicate the structure, process or outcome being measured.

**Prior Submission:**

An important consideration for avoiding bleeding and thromboembolic events in patients on warfarin therapy is maintaining the patient's International Normalized Ratio (INR) within the therapeutic range through appropriate and timely INR monitoring and dose adjustment. The recommended range of INR values is 2 to 3 for most conditions treated with warfarin, including deep venous thrombosis, pulmonary embolus, tissue heart valves, atrial fibrillation, and recurrent systemic embolism (Holbrook et al., 2012). The authors of the 2012 American College of Chest Physicians guidelines for antithrombotic therapy and prevention of thrombosis recommend INR monitoring frequency of up to 12 weeks for patients with stable INRs (Holbrook et al., 2012). The latest American College of Cardiology/American Heart Association guidelines continue to recommend INR monitoring on a monthly basis for patients with atrial fibrillation when anticoagulation is stable (Anderson et al., 2013). This measure adopts a conservative approach to INR monitoring of individuals on warfarin by using a 56-day interval, chosen “because a gap of 56 days is traditionally understood to indicate a lack of monitoring, and a period across which TTR is not interpolated” (Rose et al., 2013).

The measure focus is on establishing a minimal INR monitoring interval for the majority of patients on warfarin in the measure denominator. Warfarin has a narrow therapeutic range and therefore, requires regular monitoring with the International Normalized Ratio (INR) test and dose adjustment for the patient to stay within the therapeutic range and avoid thromboembolism or bleeding complications.

Links of Process 🡪 Health Outcome

Regular monitoring of patients on warfarin with the International Normalized Ratio (INR) test 🡪 More time within the therapeutic range of warfarin 🡪 Fewer bleeding and thromboembolic events 🡪 Lower hospitalization rates and lower mortality rates

Summary

The desired outcome for this measure is fewer bleeding and thromboembolic events in individuals on warfarin. More regular INR monitoring of patients on warfarin should result in more time in the therapeutic range, resulting in fewer bleeding and thromboembolic events and thus, fewer hospitalizations and deaths.

Citations for 1a.3

Anderson, J. L., Halperin, J. L., Albert, N. M., Bozkurt, B., Brindis, R. G., Curtis, L. H., . . . Shen, W. K. (2013). Management of patients with atrial fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation, 127*, 1916-1926.

Holbrook, A., Schulman, S., Witt, D. M., Vandvik, P. O., Fish, J., Kovacs, M. J., . . . Guyatt, G. H. (2012). Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 141*(2), e152S-e184S.

Rose, A. J., Miller, D. R., Ozonoff, A., Berlowitz, D. R., Ash, A. S., Zhao, S., . . . Hylek, E. M. (2013). Gaps in monitoring during oral anticoagulation: Insights into care transitions, monitoring barriers, and medication nonadherence. *Chest, 143*(3), 751-757.

**Updated Evidence:**

The primary indications for warfarin are prophylaxis and treatment of venous thromboembolism (VTE) and thromboembolic complications associated with atrial fibrillation.[1] Clinical practice guidelines recommend regular INR monitoring for patients taking warfarin. The 2012 clinical practice guideline from the American College of Chest Physicians (CHEST) suggests an INR testing interval of up to 12 weeks for patients with consistently stable INRs.[2] For patients with previously stable therapeutic INRs who present with a single out-of-range INR of less than or equal to 0.5 below or above therapeutic, the CHEST guideline suggests continuing the current dose and testing the INR within 1 to 2 weeks. In the 2014 guideline from the American College of Cardiology/American Heart Association Task Force for the management of patients with atrial fibrillation, patients are recommended to have INR testing at least monthly when anticoagulation is stable.[3]

Although the guidelines all note that regular INR monitoring is required, the recommended interval for monitoring varies. The CHEST guideline specifically states that “the appropriate length of the recall interval depends on the duration of prior stability and foreseeable future changes in medications or disorders that affect the INR.”[2] Studies have shown that maintaining INR stability is challenging. One study found that among patients who reached time in therapeutic range (TTR) ≥ 80% during the first six months, only 42% maintained TTR ≥ 80% during the subsequent 12 months.[4] Another study based on a Canadian cohort noted similar results in examining patients who achieved a TTR > 65% in the first six months of warfarin therapy; only about half remained on warfarin and continued to have good control (TTR > 65%) for months 7 to 12.[5] Given the difficulty in maintaining optimal TTR, the majority of patients taking warfarin are not likely suitable candidates for extended 12-week INR monitoring. Therefore, this measure continues to adopt a conservative approach to INR monitoring of individuals on warfarin by using a 56-day interval (i.e., one INR testing at least every 8 weeks).

The 56-day interval is chosen based on evidence linking to INR control without the burden of excessive testing placed on providers and patients. A large study conducted with 56,490 patients in the Veterans Health Administration (VA) demonstrated a link between gaps in the INR monitoring interval of greater than 56 days and a decrease in TTR. At the patient level, TTR for patients with ≥2 gaps per year was 10 percentage points lower than patients without gaps. At the facility-level, for each gap per patient-year, there was an associated 9.2 percentage point decrease in the facility-level TTR (p<0.001).[6] The monitoring interval of 6 to 8 weeks has also been demonstrated to provide similar INR control as the 4-week interval. A study of 890 patients from six anticoagulant clinics found that the proportion of out-of-range INR results is comparable between patients with and without extended interval monitoring (27.3% vs. 28.4%, p=0.46). The same observation was noted for the extreme out-of-range INR (≤ 1.5 or ≥ 4.0), which was 6.4% vs. 7.7% (p=0.11).[7] .

The linkage between the 56-day monitoring interval and INR control is important because INR variability and TTR are associated with clinical outcomes and healthcare resource utilization. A recent study of 127,385 US veterans provides support for this process-outcome linkage: “Patients with TTR <65% had a higher risk for any stroke/SE [systemic embolism] (HR: 1.57; 95% CI: 1.41–1.75), major bleeding (HR: 2.78; 95% CI: 2.55–3.03) and all-cause mortality (HR: 1.73; 95% CI: 1.67–1.79).”[8] These findings are similar to another study that found that INR variability was shown to be a predictor of mortality and TTR was correlated with patient survival time.[9,10] Lastly, significantly higher stroke-related healthcare costs[11] and total healthcare costs were associated with patients with low TTR (<60%) than those with high TTR.[11,12]

Given the variation in INR monitoring interval recommendations and the evidence suggesting room for improvement in anticoagulation management, this measure supports anticoagulation management through INR monitoring by specifying an evidenced-based interval of 56 days (8 weeks).

Links of Process 🡪 Health Outcome

Regular monitoring of patients on warfarin with the International Normalized Ratio (INR) test 🡪 More time within the therapeutic range of warfarin 🡪 Fewer bleeding and thromboembolic events 🡪 Lower hospitalization rates and lower mortality rates

Citations:

1. Coumadin US Full Prescribing Information. Bristol-Myers Squibb. https://packageinserts.bms.com/pi/pi\_coumadin.pdf Accessed August 22, 2018.
2. Holbrook, A., Schulman, S., Witt, D. M., Vandvik, P. O., Fish, J., Kovacs, M. J., Guyatt, G. H. (2012). Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 141*(2), e152S-e184S.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology.* 2014;64(21):e1-76. doi: 10.1016/j.jacc.2014.03.022.
4. Pokorney SD, Simon DN, Thomas L, et al. Stability of International Normalized Ratios in Patients Taking Long-term Warfarin Therapy. *JAMA.* 2016;316(6):661-663. doi: 10.1001/jama.2016.9356..
5. McAlister FA, Wiebe N, Hemmelgarn BR. Time in therapeutic range and stability over time for warfarin users in clinical practice: a retrospective cohort study using linked routinely collected health data in Alberta, Canada. *BMJ Open.* 2018;8(1):e016980. doi: 10.1136/bmjopen-2017-016980.
6. Rose AJ, Miller DR, Ozonoff A, et al. Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence. *Chest.* 2013;143(3):751-757. doi: 10.1378/chest.12-1119.
7. Barnes GD, Kong X, Cole D, et al. Extended International Normalized Ratio testing intervals for warfarin-treated patients. *J Thromb Haemost.* 2018;16(7):1307-1312. doi: 10.1111/jth.14150.
8. Liu S, Li X, Shi Q, et al. Outcomes associated with warfarin time in therapeutic range among US veterans with nonvalvular atrial fibrillation. *Curr Med Res Opin.* 2018;34(3):415-421. doi: 10.1080/03007995.2017.1384370.
9. Vanerio G. International Normalized Ratio Variability: A Measure of Anticoagulation Quality or a Powerful Mortality Predictor. *J Stroke Cerebrovasc Dis.* 2015;24(10):2223-2228. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.017.
10. Labaf A, Sjalander A, Stagmo M, Svensson PJ. INR variability and outcomes in patients with mechanical heart valve prosthesis. *Thromb Res.* 2015;136(6):1211-1215. doi: 10.1016/j.thromres.2015.10.044.
11. Deitelzweig S, Evans M, Hillson E, et al. Warfarin time in therapeutic range and its impact on healthcare resource utilization and costs among patients with nonvalvular atrial fibrillation. *Curr Med Res Opin.* 2016;32(1):87-94. doi: 10.1185/03007995.2015.1103217.
12. Nelson WW, Wang L, Baser O, Damaraju CV, Schein JR. Out-of-range international normalized ratio values and healthcare cost among new warfarin patients with non-valvular atrial fibrillation. *Journal of medical economics.* 2015;18(5):333-340. doi: 10.3111/13696998.2014.1001851.

**1a.3 Value and Meaningfulness:** **IF** this measure is derived from patient report, provide evidence that the target population values the measured ***outcome, process, or structure*** and finds it meaningful. (Describe how and from whom their input was obtained.)

**\*\*RESPOND TO ONLY ONE SECTION BELOW -EITHER 1a.2, 1a.3 or 1a.4) \*\***

**1a.2** **FOR OUTCOME MEASURES including PATIENT REPORTED OUTCOMES - Provide empirical data demonstrating the relationship between the outcome (or PRO) to at least one healthcare structure, process, intervention, or service.**

**1a.3. SYSTEMATIC REVIEW(SR) OF THE EVIDENCE (for intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measures, including those that are instrument-based) If the evidence is not based on a systematic review go to section 1a.4) If you wish to include more than one systematic review, add additional tables.**

**What is the source of the systematic review of the body of evidence that supports the performance measure? A systematic review is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data. (IOM)**

x Clinical Practice Guideline recommendation (with evidence review)

☐ US Preventive Services Task Force Recommendation

x Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*)

☐ Other

**Prior Submission:**

When the measure was last submitted, some of the questions in the table below were not included in the evidence form. The current submission includes the addition of this information into the evidence form. All updates are presented below in red text.

|  |  |
| --- | --- |
| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Title: Management of patients with atrial fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): A report of the American College of Cardiology/American Heart Associations Task Force on Practice Guidelines  Authors: Jeffrey L. Anderson, Jonathan L. Halperin, Nancy M. Albert, Biykem Bozkurt, Ralph G. Brindis, Lesley H. Curtis, David DeMets, Robert A. Guyton, Judith S. Hochman, Richard J. Kovacs, E. Magnus Ohman, Susan J. Pressler, Frank W. Sellke, Win-Kuang Shen  Date: May 6, 2013  Citation: Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2013;61(18):1935-1944. doi: 10.1016/j.jacc.2013.02.001. (page 1918)  URL: <https://www.ncbi.nlm.nih.gov/pubmed/23558044> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | “5. INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.” |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | (definitions provided in Fuster et al., 2011):  Class I = Benefit >>> Risk. Procedure/Treatment SHOULD be performed/administered.  Evidence Level: A - Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses. |
| Provide all other grades and definitions from the evidence grading system | (definitions provided in Fuster et al., 2011):  Level B = Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.  Level C = Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care. |
| Grade assigned to the **recommendation** with definition of the grade | (definitions provided in Fuster et al., 2011):  Recommendation: Class I - Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses. |
| Provide all other grades and definitions from the recommendation grading system | (definitions provided in Fuster et al., 2011):  Class IIa = Benefit >> Risk. Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/administer treatment.  Class IIb = Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment MAY BE CONSIDERED.  Class III No Benefit = Procedure/Test is not helpful. Treatment has no proven benefit.  Class III Harm = Procedure/Test entails excess cost without benefit or is harmful. Treatment is harmful to patients. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Quantity of studies on which the recommendation was made: N/A  Quality: Evidence Level: A - Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.  Methods Notes:  “This document is a compilation of the current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) practice guideline recommendations for atrial fibrillation (AF) from the “ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation,” the “2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline)”, and the “2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran).” Updated and new recommendations from 2011 are noted and outdated recommendations have been removed. No new evidence was reviewed, and no recommendations included herein are original to this document. The ACCF/AHA Task Force on Practice Guidelines chooses to republish the recommendations in this format to provide the complete set of practice guideline recommendations in a single resource.” |
| Estimates of benefit and consistency across studies | The article did not discuss benefit and consistency across studies related to INR monitoring. |
| What harms were identified? | The article did not discuss harms related to INR monitoring. |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | Fuster, V., Ryden, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Wann, L. S. (2011). Management of patients with atrial fibrillation: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Journal of the American College of Cardiology, 57*(11), e101-198.  See below (Oake et. al., 2008) for additional citations. |

**Prior Submission:**

When the measure was last submitted, some of the questions within the table below were not included in the evidence form. The current submission includes the addition of this information into the evidence form. All updates are presented below in red text.

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Title: Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines  Authors: Anne Holbrook, Sam Schulman, Daniel M. Witt, Per Olav Vandvik, Jason Fish, Michael J. Kovacs, Peter J. Svensson, David L. Veenstra, Mark Crowther, and Gordon H. Guyatt  Date: January 23, 2012  Citation: Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e152S-184S. doi: 10.1378/chest.11-2295. (page e153S)  URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278055/> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | “3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks” |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | (definitions provided in Guyatt et al., 2012):  Grade 2B: Weak recommendation, moderate-quality evidence |
| Provide all other grades and definitions from the evidence grading system | (definitions provided in Guyatt et al., 2012):  Grade 1A: Strong recommendation, high-quality evidence  Grade 1B: Strong recommendation, moderate-quality evidence  Grade 1C: Strong recommendation, low- or very-low-quality evidence  Grade 2A: Weak recommendation, high-quality evidence  Grade 2C: Weak recommendation, low- or very-low-quality evidence |
| Grade assigned to the **recommendation** with definition of the grade | (definition provided in Guyatt et al., 2012):  Grade 2B: Weak recommendation, moderate-quality evidence |
| Provide all other grades and definitions from the recommendation grading system | (definitions provided in Guyatt et al., 2012):  Grade 1A: Strong recommendation, high-quality evidence  Grade 1B: Strong recommendation, moderate-quality evidence  Grade 1C: Strong recommendation, low- or very-low-quality evidence  Grade 2A: Weak recommendation, high-quality evidence  Grade 2C: Weak recommendation, low- or very-low-quality evidence |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Quantity of studies on which the recommendation was made: n=3  Quality: Grade 2B: Weak recommendation, moderate-quality evidence  Methods notes:  “The methods for the development of this article’s recommendations follow those developed for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Although we aimed to summarize and use randomized controlled trial (RCT) evidence to inform recommendations for clinicians, we found only lower-quality evidence to address most of our questions. At the onset of our review process, our panel decided to limit the recommendations to questions in which evidence met a minimum threshold for quality: at least one comparative study with ≥ 50 patients per group with contemporaneous or historical controls reporting on patient-important outcomes or closely related surrogates. Despite this low threshold, evidence was unavailable for several important clinical management questions. When randomized trials were available, confidence in estimates often decreased because of indirectness (surrogate outcomes) and imprecision (wide CIs).” |
| Estimates of benefit and consistency across studies | “For patients receiving traditional laboratory-based INR monitoring, retrospective studies have found increasing INR recall intervals associated with both increased and decreased time in therapeutic range (TTR). Other observational studies have suggested that for patients who demonstrate a consistent pattern of stable therapeutic INRs, allowing INR recall intervals of up to 8 weeks would not result in increased risk for bleeding or thromboembolism.Three RCTs have evaluated the effectiveness of INR recall intervals exceeding the traditional North American standard of 4 weeks. One study compared 6- to 4-week recall intervals, whereas another evaluated a flexible approach that allowed recall intervals of up to 12 weeks based on several factors, including the number of prior INRs, longitudinal INR variability, and the risk of adverse events expressed as a function of the INR. The third study compared 4- to 12-week recall intervals using a blinded design. None of the studies found a difference in rates of thromboembolism, bleeding, or INR control. The appropriate length of the recall interval depends on the duration of prior stability and foreseeable future changes in medications or disorders  that affect the INR.” |
| What harms were identified? | “None of the studies found a difference in rates of thromboembolism, bleeding, or INR control. The appropriate length of the recall interval depends on the duration of prior stability and foreseeable future changes in medications or disorders  that affect the INR.” |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | Guyatt, G. H., Norris, S. L., Schulman, S., Hirsh, J., Eckman, M. H., Akl, E. A., . . . Schünemann, H. J. (2012). Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest,141*(2\_suppl), 53S-70S.  See below (Oake et. al., 2008) for additional citations. |

**Prior Submission:**

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Title: Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: A systematic review and meta-analysis.  Authors: Natalie Oake, Alison Jennings, Alan J. Forster, Dean Fergusson, Steve Doucette, & Carl van Walraven  Date: July 29, 2008  Citation: Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2008;179(3):235-244. doi: 10.1503/cmaj.080171.  URL: <http://www.cmaj.ca/content/179/3/235.long> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | The authors examined evidence as to the risk of hemorrhagic (bleeding) and thromboembolic outcomes associated with levels of the international normalized ratio (INR) that are above and below the recommended range of 2-3. The meta-analysis used person-year data to calculate the relative risk (RR) of hemorrhage and/or thromboembolic event with an INR between 3 and 5, above 5, and below 2, compared to a reference group in the range of 2-3.  Effect on Hemorrhagic Events  The meta-analysis found that the relative risk of a hemorrhagic event was 2.7 (95% CI: 1.8-3.9) for patients with an INR between 3 and 5 and 21.8 (95% CI: 12.1-39.4) for patients with an INR above 5, compared to those with an INR of 2-3 (the reference group). The relative risks for patients with an INR between 3 and 5 and above 5 were statistically significantly different from those with an INR of 2-3. The above relative risks “translated to absolute risks (and 95% CIs) of 3.7% [per year] (2.2% - 6.3%) for INRs between 3 and 5 and 30.1% [per year] (14.9% - 60.9%) for INRs above 5.” These absolute risks can be compared to an absolute risk of 1.4% per year (0.9% - 2.3%) for INRs between 2 and 3.  For hemorrhagic events, the relative risks for patients with an INR between 3 and 5, ranged from 0.5 to 11.1 across the 17 individual studies, and for patients with an INR above 5, the relative risks ranged from 4.0 to 161.3. Again, all relative risks are in relation to an INR between 2 and 3. Three studies did not report relative risks for patients with an INR above 5.  Effect on Thromboembolic Events  The meta-analysis found that the relative risk of a thromboembolic event was 3.5 (95% CI: 2.8–4.4; p<0.01) for patients with an INR less than 2, and 2.6 (95% CI: 1.3–5.1;p<0.01) for patients with an INR above 5, compared to those with an INR of 2-3 (the reference group). The relative risks for patients with an INR less than 2 and above 5 were statistically significantly different from those with an INR of 2-3. These relative risks represent absolute risks (and 95% CIs) of 9.0% per year (6.1% - 13.4%) for INRs less than 2 and 6.6% per year (3.2% -13.9%) for INRs above 5. These absolute risks can be compared to an absolute risk of 2.6% per year (1.8% - 3.6%) for INRs between 2 and 3.  For thromboembolic events, the relative risks for patients with an INR less than 2 ranged from 0.0 to 10.9 across the 17 individual studies, and for patients with an INR above 5, the relative risks ranged from 0.0 to 9.0. Again, all relative risks are in relation to an INR between 2 and 3. Six studies did not report relative risks for patients with an INR above 5. |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | There was no grade assigned for the quality of quoted evidence. |
| Provide all other grades and definitions from the evidence grading system | Because there was no grade assigned for the quality of quoted evidence, this information is not available. |
| Grade assigned to the **recommendation** with definition of the grade | There was no grade assigned for the quality of quoted evidence. |
| Provide all other grades and definitions from the recommendation grading system | Because there was no grade assigned for the quality of quoted evidence, this information is not available. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Quantity of studies on which the recommendation was made: n=19  Quality: not described.  Methods notes:  Of the 19 studies included in the systematic review, 10 were retrospective cohort studies, six were randomized controlled trials, and three were prospective cohort studies. |
| Estimates of benefit and consistency across studies | Effect on Hemorrhagic Events  The meta-analysis found that the relative risk of a hemorrhagic event was 2.7 (95% CI: 1.8-3.9) for patients with an INR between 3 and 5 and 21.8 (95% CI: 12.1-39.4) for patients with an INR above 5, compared to those with an INR of 2-3 (the reference group). The relative risks for patients with an INR between 3 and 5 and above 5 were statistically significantly different from those with an INR of 2-3. The above relative risks “translated to absolute risks (and 95% CIs) of 3.7% [per year] (2.2% - 6.3%) for INRs between 3 and 5 and 30.1% [per year] (14.9% - 60.9%) for INRs above 5.” These absolute risks can be compared to an absolute risk of 1.4% per year (0.9% - 2.3%) for INRs between 2 and 3.  For hemorrhagic events, the relative risks for patients with an INR between 3 and 5, ranged from 0.5 to 11.1 across the 17 individual studies, and for patients with an INR above 5, the relative risks ranged from 4.0 to 161.3. Again, all relative risks are in relation to an INR between 2 and 3. Three studies did not report relative risks for patients with an INR above 5.  Effect on Thromboembolic Events  The meta-analysis found that the relative risk of a thromboembolic event was 3.5 (95% CI: 2.8–4.4; p<0.01) for patients with an INR less than 2, and 2.6 (95% CI: 1.3–5.1;p<0.01) for patients with an INR above 5, compared to those with an INR of 2-3 (the reference group). The relative risks for patients with an INR less than 2 and above 5 were statistically significantly different from those with an INR of 2-3. These relative risks represent absolute risks (and 95% CIs) of 9.0% per year (6.1% - 13.4%) for INRs less than 2 and 6.6% per year (3.2% -13.9%) for INRs above 5. These absolute risks can be compared to an absolute risk of 2.6% per year (1.8% - 3.6%) for INRs between 2 and 3.  For thromboembolic events, the relative risks for patients with an INR less than 2 ranged from 0.0 to 10.9 across the 17 individual studies, and for patients with an INR above 5, the relative risks ranged from 0.0 to 9.0. Again, all relative risks are in relation to an INR between 2 and 3. Six studies did not report relative risks for patients with an INR above 5. |
| What harms were identified? | Monitoring INR values and titrating warfarin therapy only requires drawing blood and patient counseling and therefore is not generally associated with harms. |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | The systematic review concluded, "The risks of hemorrhage and thromboemboli are minimized at international normalized ratios of 2–3. Ratios that are moderately higher than this therapeutic range appear safe and more effective than subtherapeutic ratios." Since the publication of the systematic review, we identified six additional studies that support the conclusions of the systematic review and additionally provide evidence that the frequency of INR monitoring is associated with both improved intermediate outcomes (i.e., time in the therapeutic range) and increased risk of thromboembolic events.  Citations:  Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ.* 2013;185(2):E121-127. doi: 10.1503/cmaj.121218.  Inoue H, Okumura K, Atarashi H, et al. Target international normalized ratio values for preventing thromboembolic and hemorrhagic events in Japanese patients with non-valvular atrial fibrillation: results of the J-RHYTHM Registry. *Circ J.* 2013;77(9):2264-2270.  Rose AJ, Ozonoff A, Henault LE, Hylek EM. Warfarin for atrial fibrillation in community-based practise. *J Thromb Haemost.* 2008;6(10):1647-1654.  Rose AJ, Miller DR, Ozonoff A, et al. Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence. *Chest.* 2013;143(3):751-757. doi: 10.1378/chest.12-1119.  Witt DM, Delate T, Clark NP, et al. Nonadherence with INR monitoring and anticoagulant complications. *Thromb Res.* 2013;132(2):e124-130. doi: 10.1016/j.thromres.2013.06.006.  Witt DM, Delate T, Clark NP, et al. Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users. *J Thromb Haemost.* 2010;8(4):744-749. doi: 10.1111/j.1538-7836.2010.03756.x. |

**Updated Evidence:**

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Title: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.  Authors: Craig T. January, L. Samuel Wann, Joseph S. Alpert, Hugh Calkins, Joaquin E. Cigarroa, Joseph C. Cleveland Jr., Jamie B. Conti, Patrick T. Ellinor, Michael D. Ezekowitz, Michael E. Field, Katherine T. Murray, Ralph L. Sacco, William G. Stevenson, Patrick J. Tchou, Cynthia M. Tracy and Clyde W. Yancy  Date: December 2, 2014  Citation: January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology.* 2014;64(21):e1-76. doi: 10.1016/j.jacc.2014.03.022. *(page 2251)*  URL: <http://www.onlinejacc.org/content/64/21/e1> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | “*6. Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable.”* |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses. |
| Provide all other grades and definitions from the evidence grading system | Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.  Level of Evidence C: Consensus opinion of experts, case studies, or standard of care. |
| Grade assigned to the **recommendation** with definition of the grade | Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. |
| Provide all other grades and definitions from the recommendation grading system | Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.  IIa: Weight of evidence/opinion is in favor of usefulness/efficacy  IIb: Usefulness/efficacy is less well established by evidence/opinion.  Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful. No Benefit - Procedure/Test not helpful or Treatment without established proven benefit  Harm - Procedure/Test leads to excess cost without benefit or is harmful, and or Treatment is harmful |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Quantity of studies on which the recommendation was made: n=3  Quality: Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.  Methods notes:  “An extensive evidence review was conducted, focusing on 2006 through October 2012 and selected other references through March 2014.”  “Searches were extended to studies, reviews, and other evidence conducted in human subjects, published in English, and accessible through PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline.”  “Additionally, the writing committee reviewed documents related to atrial fibrillation (AF) previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.” |
| Estimates of benefit and consistency across studies | The article did not discuss benefits or consistency across studies related to INR monitoring. |
| What harms were identified? | The article did not discuss harms related to INR monitoring. |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | Witt et al (2016) published guidance for the management of warfarin therapy. The guidance provided was based on a review of medical literature and consensus opinions of all authors and the endorsement of the Anticoagulation Forum’s Board of Directors. The guidance (below) supports an INR monitoring interval of up to 12 weeks. This guidance supports the recommendations and does not change the concussions of the systematic review by Holbrook et al. (2012). Further, Witt et al. (2016) shows the ambiguity in the appropriate length for follow-up.   * “During the first 3 months of warfarin therapy for VTE we suggest that INR recall intervals not exceed 6 weeks.” * “For patients demonstrating consistently stable INRs after 3 months of warfarin therapy for VTE we suggest that INR recall intervals can be extended up to 12 weeks.”   The additional studies cited below support the recommendations of the presented evidence that INR should be regularly monitored for patients on warfarin.  Citations:  Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *The American journal of medicine.* 2015;128(12):1300-1305 e1302. doi: 10.1016/j.amjmed.2015.05.044.  Deitelzweig S, Evans M, Hillson E, et al. Warfarin time in therapeutic range and its impact on healthcare resource utilization and costs among patients with nonvalvular atrial fibrillation. *Current medical research and opinion.* 2016;32(1):87-94. doi: 10.1185/03007995.2015.1103217.  Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *Journal of the American College of Cardiology.* 2014;63(20):2141-2147. doi: 10.1016/j.jacc.2014.02.549.  Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. *The Canadian journal of cardiology.* 2014;30(9):962-970. doi: 10.1016/j.cjca.2014.03.022.  Nelson WW, Wang L, Baser O, Damaraju CV, Schein JR. Out-of-range international normalized ratio values and healthcare cost among new warfarin patients with non-valvular atrial fibrillation. *Journal of medical economics.* 2015;18(5):333-340. doi: 10.3111/13696998.2014.1001851.  Razouki Z, Ozonoff A, Zhao S, Jasuja GK, Rose AJ. Improving quality measurement for anticoagulation: adding international normalized ratio variability to percent time in therapeutic range. *Circulation Cardiovascular quality and outcomes.* 2014;7(5):664-669. doi: 10.1161/CIRCOUTCOMES.114.000804.  Rose AJ, Park A, Gillespie C, et al. Results of a regional effort to improve warfarin management. *Annals of Pharmacotherapy.* 2017. doi: 10.1177/1060028016681030.  Schein JR, White CM, Nelson WW, Kluger J, Mearns ES, Coleman CI. Vitamin K antagonist use: evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thromb J.* 2016;14:14. doi: 10.1186/s12959-016-0088-y.US Department of Health and Human Services. National action plan for adverse drug event prevention. Washington, DC: US Department of Health & Human Services Office of Disease Prevention and Health Promotion; 2014. <http://health.gov/hcq/ade-action-plan.asp>. Accessed November 17, 2015. |

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**1a.4 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.4.1** **Briefly SYNTHESIZE the evidence that supports the measure.** A list of references without a summary is not acceptable.

**1a.4.2 What process was used to identify the evidence?**

**1a.4.3.** **Provide the citation(s) for the evidence.**