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

**Measure Title**: INR for Individuals Taking Warfarin and Interacting Anti-Infective Medications

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

**Date of Submission**: 1/16/2014

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| **Instructions**  *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.*   * Respond to all questions as instructed with answers immediately following the question. 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. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * 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 Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**  **Subcriterion 1a.** **Evidence to Support the Measure Focus**  The measure focus is a health outcome or is evidence-based, demonstrated as follows:   * Health outcome:[**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. * Intermediate clinical outcome, Process,[**4**](#Note4) or Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence[**5**](#Note5)that the measure focus leads to a desired health outcome. * Patient experience with care: evidence that the measured aspects of care are those valued by patients and for which the patient is the best and/or only source of information OR that patient experience with care is correlated with desired outcomes. * Efficiency:[**6**](#Note6) evidence for the quality component as noted above.   **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.** 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.  **5.** 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).  **6.** Measures of efficiency combine the concepts of resource use and quality (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**:

Outcome

☐ Health outcome:

*Health outcome includes patient-reported outcomes (PRO, i.e., HRQoL/functional status, symptom/burden, experience with care, health-related behaviors)*

Intermediate clinical outcome:

X Process: INR Monitoring Test for Individuals Taking Warfarin and Interacting Anti-Infective Medications

☐ Structure: Click here to name the structure

☐ Other: Click here to name what is being measured

**HEALTH OUTCOME PERFORMANCE MEASURE** *If not a health outcome, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the linkage between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) and at least one healthcare structure, process, intervention, or service**.

*Note: For health outcome performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the linkages between structure, process, intermediate outcome, and health outcomes**. Include all the steps between the measure focus and the health outcome.

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](#_ENREF_1_1)). Warfarin has a narrow therapeutic range and interacts with many drugs, implying that INR tests should be performed if a patient on warfarin is put on a potentially interacting drug. For example, the 2011 British Committee for Standards in Haematology guidelines on oral anticoagulation with warfarin recommend that the INR test be performed within three to five days after a potentially interacting drug is prescribed ([Keeling et al., 2011](#_ENREF_1_2)).

The measure focus is on INR monitoring of patients on warfarin and interacting anti-infectives. Some anti-infective medications are known to affect the anticoagulant effect of warfarin. Because warfarin has a narrow therapeutic range, monitoring with the INR test is required shortly after these anti-infectives are prescribed and dose adjustment is performed, if necessary, in order that the patient remains within the therapeutic range and avoids thromboembolism or bleeding complications. The measure focuses on anti-infective drugs because they are commonly used in acute care settings, which increases the risk of a possible interaction being overlooked.

Links of Process 🡪 Health Outcome

Monitoring of patients on warfarin with the INR test within three to five days after an interacting anti-infective is prescribed 🡪

Dose adjustment of warfarin, if necessary 🡪

INR value 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 who are prescribed an interacting anti-infective medication. INR monitoring within three to five days after the interacting anti-infective medication is prescribed should result in dose adjustment, if necessary, and the INR value remaining in the therapeutic range, resulting in fewer bleeding and thromboembolic events and thus, fewer hospitalizations and deaths.

Citations for 1a.3

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.

Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., . . . Makris, M. (2011). Guidelines on oral anticoagulation with warfarin–fourth edition. *British Journal of Haematology, 154*(3), 311-324.

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

X Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

☐ US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

X Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

X Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., . . . Makris, M. (2011). Guidelines on oral anticoagulation with warfarin–fourth edition. *British Journal of Haematology, 154*(3), 311-324.

<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08753.x/pdf>

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

Keeling et al. (2011). Guidelines on oral anticoagulation with warfarin–fourth edition: British Committee for Standards in Haematology (page 320):

*10.6 Drug interactions*

*Recommendations*

* **All patients on warfarin who are prescribed a drug that may interact with it should have an INR performed after 3–5 d (2C).**

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

The following definition applies to the grade used for the guideline recommendation by Keeling et al. (2011) listed in Section 1a.4.2 of this form (definition provided in British Committee for Standards in Haemotology, 2010):

**Strength of Recommendation. Weak (grade 2):** Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

**Quality of Evidence. (C) Low:** Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Note that the evidence underlying recommendations to reduce drug-drug interactions tends to be weak in general, because conducting randomized trials to study such interactions would be unethical.

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

The following is a complete set of definitions that apply to the grades used for the recommendations in the guidelines by Keeling et al. (2011) (definitions provided in British Committee for Standards in Haemotology, 2010):

From January 2010 BCSH guidelines have used the GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines ([British Committee for Standards in Haemotology, 2010](#_ENREF_4_1)). For laboratory tests guidance is related specifically to clinical utility (that is the ability of a test to alter clinical outcome). GRADE stands for: Grading of Recommendations Assessment, Development and Evaluation.  
  
STRENGTH OF RECOMMENDATIONS:

**Strong (grade 1):** Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

**Weak (grade 2):** Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

QUALITY OF EVIDENCE

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

**(A) High** Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

**(B) Moderate** Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis),or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

**(C) Low** Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

British Committee for Standards in Haemotology. (2010). *Evidence Levels and Grades of Recommendation. GRADE.* Retrieved October 31, 2013, from <http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html>

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

☐Yes **→ *complete section*** [***1a.7***](#Section1a7)

XNo **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

Multiple monographs, each entitled "Warfarin Sodium Oral (Anticoagulants) - [Specific Medication] Interaction." These monographs are available through a subscription service from:

Wolters Kluwer Health. (2013). Facts & Comparison Formulary Monograph Service™. Wolters Kluwer Health. Retrieved November 22, 2013, from <http://www.factsandcomparisons.com/formulary-monograph-service-online/>

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

The citation and URL for methodology for evidence review and grading are the same as in 1a.6.1.

***Complete section*** [***1a.7***](#Section1a7)

**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

The specific topic addressed in the evidence review was the interaction between warfarin and anti-infective medications.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

A grade was assigned for the evidence provided for each medication by the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013) that ranged from 1 (Doubtful/Unknown) to 5 (Established).

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

The following scale is used for grading the strength of the evidence (Wolters Kluwer Health, 2013):

5-Established

4-Probable

3-Suspected

2-Possible

1-Doubtful/Unknown

The following scale is used for grading the severity of the interaction (Wolters Kluwer Health, 2013):

3-Major

2-Moderate

1-Minor

0-None

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**: The time period associated with the cited studies vary by medication, but the publication dates cover 1965 through the present.

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

For each medication, information about the number and type of study designs is summarized in Table 1. This information was derived from the monographs available through the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013).

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

The quality of the evidence depends on the type of studies conducted to investigate the interaction between warfarin and each medication. For each medication, the rating of the evidence cited to support the interaction with warfarin is provided in Table 1. The evidence was rated as part of the monograph from the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013).

**Table 1. Evidence Supporting Clinical Effect of Interactions between Warfarin and Anti-Infective Medications**

**(Adapted from Drug Facts Interaction, Wolters Kluwer Health, 2013)**

| **Anti-Infective Medication** | **Anticoagulant Effect** | **Drug Facts Interaction Severity Rating\*** | **Drug Facts Interaction Documentation Rating\*\*** | **Pharmacokinetic Studies** | **Epidemiologic Studies** | **Case Reports** |
| --- | --- | --- | --- | --- | --- | --- |
| **Aminoglycosides** |  |  |  |  |  |  |
| Neomycin | Increased | Moderate | Possible | 3 studies (1965, 1970, 1976) | none | none |
| Paromomycin | Increased | Moderate | Possible | Neomycin: 3 studies (1965, 1970, 1976) | none | none |
| **Antifungals** |  |  |  |  |  |  |
| Fluconazole | Increased | Major | Established | 8 studies (1986-1993) | 1 case-control study (2008), 1 pharmacoepidemiologic study of azole antifungals (2012) | none |
| Griseofulvin | Decreased | Moderate | Probable | 2 studies (1967, 1970) | none | 1 case report (1986) |
| Itraconazole | Increased | Major | Possible | none | 1 pharmacoepidemiologic study of azole antifungals (2012) | 2 case reports (1990, 2011) |
| Ketoconazole | Increased | Major | Possible | 1 study (1982) | 1 pharmacoepidemiologic study of azole antifungals (2012) | 2 case reports (1984, 2009) |
| Miconazole Oral Gel | Increased | Major | Probable | 1 study (1992) | 1 retrospective study (2011) | 13 case reports or case series (1977-2004) |
| Miconazole Topical Gel | Increased | Major | Probable | none | none | 5 case reports or case series (2002-2010) |
| Miconazole Vag Supp | Increased | Major | Probable | none | none | miconazole topical gel:  5 case reports or case series (2002-2010) |
| Terbinafine | Increased/ Decreased | Major | Possible | none | none | 3 case reports (1998-2009) |
| Voriconazole | Increased | Major | Suspected | 1 double-blind, placebo-controlled, 2-way crossover study (2003) | none | none |
| **Anti-malarial** |  |  |  |  |  |  |
| Atovaquone | Increased | Moderate | Possible | none | none | 1 case report (2011) |
| Mefloquine | Increased | Major | Possible | none | none | 2 case reports (both in 2001) |
| Proguanil | Increased | Major | Possible | none | none | 1 case report (1991) |
| Quinine | Increased | Major | Suspected | none | none | 2 case reports (1968, 1969) |
| **Antiviral** |  |  |  |  |  |  |
| Atazanavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| Darunavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| Fosamprenavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| Indinavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| Interferon alpha | Increased | Moderate | Possible | none | none | 2 case reports (1995, 1998) |
| Interferon beta | Increased | Moderate | Possible | none | none | 1 case report (1995) |
| Nelfinavir | Increased/ Decreased | Moderate | Suspected | none | 1 retrospective study (2012), 1 case-control study (2013) | 7 case reports or case series (1998-2012) |
| Nevirapine | Decreased | Moderate | Suspected | none | none | 4 case reports (2001-2008) |
| Oseltamivir | Increased | Major | Possible | 1 study (2010) | none | 2 case series (2006, 2009) |
| Ribavirin | Decreased | Major | Possible | not applicable | not applicable | not applicable |
| Ritonavir | Increased/ Decreased | Moderate | Suspected | none | 1 retrospective study (2012), 1 case-control study (2013) | 7 case reports (1998-2012) |
| Saquinavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| Tipranavir | Increased/ Decreased | Moderate | Possible | not applicable | not applicable | not applicable |
| **Cephalosporins** |  |  |  |  |  |  |
| Cefotetan | Increased | Major | Suspected | none | Cefamandole: 1 retrospective study (1984), 1 prospective study (1987) | none |
| **Fluoroquinolones** |  |  |  |  |  |  |
| Ciprofloxacin | Increased | Major | Probable | none | 1 nested case-control study (2010), 3 controlled studies (1991-1996) | 9 case reports (1989-2000) |
| Levofloxacin | Increased | Major | Probable | 1 study (1996) | 2 retrospective reviews (2006, 2009), 1 case-control study (2005) | 5 case reports (2001-2007) |
| Moxifloxacin | Increased | Major | Probable | none | none | 4 case reports (2003-2008) |
| Norfloxacin | Increased | Major | Probable | 1 study (1990) | none | 2 case reports (1989, 1991) |
| Ofloxacin | Increased | Major | Probable | none | none | 2 case reports (1988, 1993) |
| **Macrolides** |  |  |  |  |  |  |
| Azithromycin | Increased | Major | Probable | none | 1 study and 1 retrospective study (2004, 2005), 1 case-control study (2000), 1 retrospective cohort study (2004) | 6 case reports (1996-2004) |
| Clarithromycin | Increased | Major | Probable | none | 1 study (2004) | 6 case reports (1996-2001) |
| Erythromycin | Increased | Major | Probable | 1 study (1998), 2 controlled studies (1984, 1989) | 1 study (2004) | 9 case reports (1980-2010) |
| **Penicillin** |  |  |  |  |  |  |
| Amoxicillin | Increased | Moderate | Possible | none | none | 4 case reports (1993-2001) |
| Amoxicillin/clavulanic acid | Increased | Moderate | Possible | 1 study (2011) | none | 5 case reports (1993-2009) |
| Ampicillin | Increased | Moderate | Possible | Evidence in ampicillin monograph relates to amoxicillin and amoxicillin/  clavulanic acid (see above for those results) | Evidence in ampicillin monograph relates to amoxicillin and amoxicillin/clavulanic acid (see above for those results) | Evidence in ampicillin monograph relates to amoxicillin and amoxicillin/  clavulanic acid (see above for those results) |
| Dicloxacillin | Decreased | Moderate | Probable | none | none | 6 case reports (1987-2010) |
| Nafcillin | Decreased | Moderate | Probable | none | none | 7 case reports (1984-2007) |
| Oxacillin | Increased | Moderate | Possible | Evidence in oxacillin monograph relates to amoxicillin and amoxicillin/  clavulanic acid (see above for those results) | Evidence in oxacillin monograph relates to amoxicillin and amoxicillin/clavulanic acid (see above for those results) | Evidence in oxacillin monograph relates to amoxicillin and amoxicillin/ clavulanic acid (see above for those results) |
| Penicillin G | Increased | Moderate | Possible | none | none | 1 case report (1976) |
| Piperacillin | Increased | Moderate | Possible | Evidence in piperacillin monograph relates to amoxicillin and amoxicillin/ clavulanic acid (see above for those results) | Evidence in piperacillin monograph relates to amoxicillin and amoxicillin/clavulanic acid (see above for those results) | Evidence in piperacillin monograph relates to amoxicillin and amoxicillin/ clavulanic acid (see above for those results) |
| Ticarcillin | Increased | Moderate | Possible | Evidence in ticarcillin monograph relates to amoxicillin and amoxicillin/  clavulanic acid (see above for those results) | Evidence in ticarcillin monograph relates to amoxicillin and amoxicillin/clavulanic acid (see above for those results) | Evidence in ticarcillin monograph relates to amoxicillin and amoxicillin/  clavulanic acid (see above for those results) |
| **Tetracycline** |  |  |  |  |  |  |
| Demeclocycline | Increased | Major | Suspected | none | none | Evidence in demeclo-cycline monograph relates to doxycycline (see below for those results) |
| Doxycycline | Increased | Major | Suspected | none | none | 4 case reports (1980-2007) |
| Minocycline | Increased | Major | Suspected | none | none | Evidence in minocycline monograph relates to doxycycline (see above for those results) |
| Oxytetracycline | Increased | Major | Suspected | not applicable | not applicable | not applicable |
| Tetracycline | Increased | Major | Suspected | none | none | 2 case reports (1989, 1992) |
| **Anti-infective, Misc** |  |  |  |  |  |  |
| Chloramphenicol | Increased | Major | Suspected | 2 studies (1962, 1969) | none | 1 case report (1999) |
| Isoniazid | Increased | Moderate | Possible | 1 study in dogs (1971), 1 study in rabbits (1979) | none | 1 case report (1977) |
| Metronidazole | Increased | Major | Suspected | 1 study (1976) | 1 cohort study (2006) | 3 case reports (1976-2008) |
| Rifaximin | Decreased | Moderate | Possible | none | none | 1 case report (2011) |
| Sulfamethoxazole | Increased | Major | Established | 2 controlled studies (1975, 2005), 2 studies (2007, 2008) | 2 population-based, nested, case-control studies (2008, 2010) | 9 case reports (1975-2005) |
| Sulfisoxazole | Increased | Major | Established | n/a | 3 controlled studies | 12 case reports |
| Telithromycin | Increased | Major | Probable | none | none | 2 case reports (2004, 2006) |
| Tinidazole | Increased | Major | Suspected | Evidence in tinidazole monograph relates to metronidazole (see above for those results) | Evidence in tinidazole monograph relates to metronidazole (see above for those results) | Evidence in tinidazole monograph relates to metronidazole (see above for those results) |
| **Other** |  |  |  |  |  |  |
| Rifabutin | Decreased | Major | Established | Evidence in rifabutin monograph relates to rifampin (see below for those results) | Evidence in rifabutin monograph relates to rifampin (see below for those results) | Evidence in rifabutin monograph relates to rifampin (see below for those results) |
| Rifampin (Found on Rifamycins Drug Facts) | Decreased | Major | Established | 4 studies (1974-2001) | none | 3 case reports (1974-1975) |
| Rifapentine | Decreased | Major | Established | Evidence in rifapentine monograph relates to rifampin (see above for those results) | Evidence in rifapentine monograph relates to rifampin (see above for those results) | Evidence in rifapentine monograph relates to rifampin (see above for those results) |

Source: Multiple monographs, each entitled "Warfarin Sodium Oral (Anticoagulants) - [Specific Medication] Interaction." These monographs are available through a subscription service from: Facts & Comparison Formulary Monograph Service™. (2013). Wolters Kluwer Health. Retrieved November 22, 2013, from [http://www.factsandcomparisons.com/formulary-monograph-service-online/](http://www.factsandcomparisons.com/formulary-monograph-service-online/%20)

\*The "Severity Rating" refers to the severity of the clinical reaction that might result from an interaction between warfarin and the specific medication. The severity rating is taken from the medication-specific monographs by the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013). These monographs provide a severity rating based on information available from the literature.

\*\*The "Documentation Rating" refers to the strength of the evidence as rated in the medication-specific monographs from the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013). These monographs provide measures of effect from selected epidemiologic studies, which are considered in the rating of the documentation assigned to the interaction between warfarin and the specific medication.

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

The monographs from the Facts & Comparison Formulary Monograph Service™ (Wolters Kluwer Health, 2013) provide measures of effect from the cited epidemiologic studies. This information is considered in the rating of the documentation that is assigned to the interaction in the monograph.

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

The harms that occur as a result of interactions between warfarin and the individual medications cover a wide spectrum of adverse drug reactions. However, the harms of interest for this measure are primarily related to the anticoagulation effect of warfarin that may result in bleeding events, thromboembolic events, or death.

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

**1a.8 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.*

In this section, we summarize the findings of six recent studies published in the medical literature that focus on the relationship of interactions between warfarin and anti-infective medications and adverse outcomes in patients taking the two medications.

**1a.8.1** **What process was used to identify the evidence?**

Six studies were identified using hand searches of reference lists of relevant clinical practice guidelines and other relevant articles and Web of Science citation searches of key articles. The abstracts and/or full-text articles from both types of searches were reviewed to identify those studies that addressed the relationship between interactions between warfarin and anti-infectives and adverse outcomes. The six selected studies met the following criteria: the study identified patients on warfarin who also took an anti-infective medication, the study reported patient outcomes among those taking the two medications, and the study was published in the last 10 years.

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**

Zhang, Young, & Berger (2006): In this retrospective cohort study of 17,895 patients (mean age 64.3 years) with at least one claim for warfarin between October 2003 and September 2004, 2,634 (14.7%) experienced hemorrhage within one week of receiving their prescription for warfarin. Of this cohort, 3,385 patients (18.9%) were concomitantly taking cephalosporins and 779 patients (4.4%) were taking metronidazole. Compared to the rate of hemorrhage in the overall cohort of warfarin users (14.7%) and those taking warfarin only (14.2%), those also taking cephalosporins and those taking metronidazole were at a higher risk for hemorrhage with rates of 17.2% (p<0.05) and 22.7% (p<0.05), respectively. The odds ratios (ORs) for hemorrhage were 1.16 (95% CI 1.04-1.29) in warfarin users taking cephalosporins and 1.58 (95% CI 1.32-1.89) in those taking metronidazole. In total, 2,634 patients (14.7%) experienced some type of hemorrhage, but a breakdown between those taking anti-infectives and those not taking was not provided.

Schelleman et al. (2008): In this nested case-control and case-crossover study of Medicaid data, 308,100 patients taking warfarin experienced 11,444 gastrointestinal hemorrhages requiring hospitalization (4.89 cases per 100 patient-years). Each of these cases was matched to up to 50 controls (combined samples, 33.7% male, 26.3% <60 years, 28.5% ≥80 years). Odds ratios for anti-infective drugs were calculated by identifying patients experiencing bleeds within six to ten days after filling a prescription for anti-infectives, since it takes five days for most anti-infective drugs to reach steady state concentrations. For each drug examined, the risk of a gastrointestinal hemorrhage after a fill of an anti-infective based on ORs was significantly higher, except for amoxicillin: ciprofloxacin 1.58 (95% CI 1.22-2.04), levofloxacin 1.64 (95% CI 1.31-2.04), gatifloxacin 2.10 (95% CI 1.07-4.11), cotrimoxazole 2.70 (95% CI 2.14-3.41), fluconazole 2.23 (95% CI 1.49-3.33), cephalexin 1.37 (95% CI 1.05-1.80), and amoxicillin 1.28 (95% CI 0.99-1.65). However, most ORs for bleeds within zero to five days of filling an anti-infective prescription exceeded those at six to 10 days: ciprofloxacin 2.14 (95% CI 1.76-2.62), levofloxacin 2.48 (95% CI 2.10-2.93), gatifloxacin 3.02 (95% CI 1.81-5.03), cotrimoxazole 1.56 (95% CI 1.19-2.06), fluconazole 1.66 (95% CI 1.09-2.53), cephalexin 1.72 (95% CI 1.38-2.16), and amoxicillin 1.47 (95% CI 1.17-1.84). Controlling for indication by using cephalexin, a drug not classified as potentially interacting with warfarin, the authors found significant associations only with cotrimoxazole at six to ten days (adjusted OR 1.66, 95% CI 1.01-2.74) and fluconazole at 11 to 15 days (adjusted OR 2.59, 95% CI 1.18-5.69). They suggest that the observed increased risk of hemorrhage in patients taking warfarin and an antibiotic may be partially due to the underlying infection rather than an interaction between warfarin and the anti-infective.

Penning-van Beest, Koerselman, & Herings (2008): This retrospective cohort study of 59,987 patients (age range: 40-80 years) taking acenocoumarol or phenprocoumon determined relative risk of bleeding for those patients concurrently taking an antibiotic, based on pharmacy dispensing data and hospital discharge data for 1996-2004. A total of 1,850 patients were hospitalized for bleeding during the study, of which 73 patients were taking coumarin and an antibiotic. Patients on coumarin also taking cefradine had the greatest risk of bleeding with relative risks (RR) of 53.4 (95% CI 17.2-166.1), followed by patients taking neomycin, who had RR of 43.4 (95% CI 6.1-308.6). Other antibiotics also showed increased risk of bleeding: amoxicillin/clavulanic acid 4.7 (95% CI 2.8-7.9), doxycycline 2.6 (95% CI 1.4-4.8), amoxicillin 3.0 (95% CI 1.6-5.8), ciprofloxacin 3.9 (95% CI 1.8-8.2), cotrimoxazole 5.3 (95% CI 2.4-11.8), pheneticillin 4.6 (95% CI 1.2-18.5), and tetracycline 8.7 (95% CI 1.2-62.0). All but one of the rest of the antibiotics showed an increased risk of hemorrhage, but not significantly greater than 1.0: flucloxacillin 2.2 (95% CI 0.7-6.9), norfloxacin 2.2 (95% CI 0.7-6.7), ofloxacin 2.8 (95% CI 0.7-11.3), nitrofurantoin 0.8 (95% CI 0.2-3.2), trimethoprim 1.3 (95% CI 0.3-5.4), clarithromycin 1.8 (95% CI 0.4-7.0), azithromycin 4.1 (95% CI 1.0-16.2), eythromycin 4.2 (95% CI 0.6-29.5), phenoxymethylpenicillin 4.7 (95% CI 0.7-33.2), benzathinebenzylpenicillin 5.8 (95% CI 0.8-41.5).

Fischer, Juurlink, Mamdani, Kopp & Laupacis (2010): In this population-based, nested case-control study of 134,637 patients (median age 80 years) taking warfarin, cases of upper gastrointestinal bleeding were matched to up to 10 controls and compared using claims data for 1997-2007. Of the antibiotics examined, cases were more likely than controls to be taking cotrimoxazole (adjusted OR 3.84, 95% CI 2.33-6.33) and ciprofloxacin (adjusted OR 1.94, 95% CI 1.28-2.95). The number of patients on warfarin experiencing bleeding complications on different antibiotics ranged from five on norfloxacin to 31 on ciprofloxacin. Other antibiotics examined did not exhibit a significant increase in bleeding when compared to patients not taking them, including amoxicillin or ampicillin (adjusted OR 1.37, 95% CI 0.92-2.05), nitrofurantoin (adjusted OR 1.40, 95% CI 0.71-2.75), norfloxacin (adjusted OR 0.38, 95% CI 0.12-1.26), and ocular antibiotics (adjusted OR 0.99, 95% CI 0.50-1.93).

Jobski, Behr, & Garbe (2011): In this nested case-control study in a cohort of 246,220 German patients (mean age 67.6 years) taking phenprocoumon based on claims data, the most frequently used vitamin K antagonist in Germany, patients taking antibiotic drugs concurrently with phenprocoumon saw increased risk of hemorrhage. A total of 2,553 patients required hospitalization for bleeding, with the number of patients taking specific antibiotics ranging from six taking ofloxacin to 37 taking ciprofloxacin. These "cases" were matched to 25,348 controls. Specifically, adjusted ORs were 2.74 (95% CI 1.80-4.18) for ciprofloxacin, 4.40 (95% CI 2.45-7.89) for levofloxacin, 2.99 (95% CI 1.39-6.42) for amoxicillin plus clavulanic acid, and 3.57 (95% CI 2.36-5.40) for cotrimoxazole. The study also examined the effect of other medications on bleeding events; since these medications are not anti-infectives, the results are not included here.

Baillargeon et al. (2012): In this case-control study nested within a cohort of 38,762 patients, continuous warfarin users were monitored for a year or until hospitalization from a bleeding event using claims data. Patients experiencing bleeding events (gastrointestinal, nongastrointestinal, intracranial, and general warfarin toxicity) (N=798; 34.5% male, 10.8% <70 years, 25.8% ≥85 years) were matched with controls from the cohort (N=2,394; 35.0% male, 10.3% <70 years, 25.4% ≥85 years). Patients on warfarin who were exposed to any antibiotic were twice as likely as those not exposed to an antibiotic to have a bleeding event that required hospitalization (adjusted OR 2.01, 95% CI 1.62-2.50), with higher risk of non-GI bleeding compared to GI bleeding, with adjusted ORs of 2.49 (95% CI 1.88-3.30) and 1.68 (95% CI 1.28-2.21), respectively. Use of specific antibiotics increased the risk of bleeding, with azole antifungals, macrolides, quinolones, cotrimoxazole, penicillins, and cephalosporins having adjusted ORs of 4.57 (95% CI 1.90-11.03), 1.86 (95% CI 1.08-3.21), 1.69 (95% CI 1.09-2.62), 2.70 (95% CI 1.46-5.05), 1.92 (95% CI 1.21-2.07), and 2.45 (95% CI 1.52-3.95), respectively. There were a total of 1,136 patients with bleeding complications; the number of bleeding cases taking different classes of antibiotics ranged from 17 for azole antifungals to 40 for quinolones.

Citations for 1a.8.2

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