



Maximum Fair Price (MFP) Explanation for Xarelto

Introduction

In August 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169) into law. For the first time, the law provides Medicare with the ability to directly negotiate the prices of certain high expenditure, single source drugs without generic or biosimilar competition. On March 15, 2023, the Centers for Medicare & Medicaid Services (CMS) issued [initial guidance](#) for the Medicare Drug Price Negotiation Program (the “Negotiation Program”), including requests for public comment on key elements. On June 30, 2023, CMS issued [revised guidance](#) detailing the requirements and parameters of the Negotiation Program for the first cycle of negotiations.¹ CMS engaged in negotiations with participating manufacturers between October 1, 2023 and August 1, 2024. These negotiations resulted in agreements establishing prices (which the IRA refers to as “maximum fair prices” or “MFPs”) that will be effective beginning in 2026 (the first cycle of negotiations is referred to as negotiations for “initial price applicability year 2026” because any agreed-upon prices will be effective in 2026). CMS published the agreed-upon MFPs on August 15, 2024.

The MFP explanation for Xarelto for the agreed-upon MFP that resulted from the negotiations for initial price applicability year 2026 with Janssen Pharms, the manufacturer of Xarelto (the “Primary Manufacturer”), provides information about the negotiations for Xarelto. This information includes CMS’ perspective on the data considered that had the greatest impact in CMS’ determination of offers and consideration of counteroffers during the negotiation process through which the parties reached agreement on an MFP.² In some respects, the Primary Manufacturer had a different perspective on the relevant data. The parties to the negotiation had productive exchanges during the negotiation meetings described below in which they discussed their respective views, and these exchanges resulted in the exchange of offer(s) and counteroffer(s) among the parties and, ultimately, an agreed-upon MFP for Xarelto.

On the basis of the factors described below and the related considerations and evidence, CMS negotiated with the Primary Manufacturer in good faith and consistent with the requirements of the law on behalf of people with Medicare and the Medicare program. Throughout the negotiation process and in accordance with the IRA, CMS’ goal was to achieve agreement with the Primary Manufacturer on the lowest possible MFP for Xarelto that would be consistent with the process defined in the IRA for these price negotiations. CMS believes that the agreed-upon MFP achieves this aim. The negotiation process

¹ The [Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026](#), is referred to throughout this document as the revised guidance.

² Section 1195(a)(2) of the Social Security Act (the “Act”) requires CMS to publish an explanation for the MFP with respect to the factors as applied under section 1194(e) for each selected drug. The MFP explanation is discussed in section 60.6.1 of the [revised guidance](#).

ended in both parties agreeing to an MFP of \$197.00 for Xarelto by the conclusion of the negotiation period on August 1, 2024.³ The agreed-upon MFP is set to take effect on January 1, 2026.

The MFP explanation contains the following components:

- MFP Explanation Narrative for Xarelto
 - Summary of the Negotiation Process
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 - Manufacturer-Specific Data
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 - Therapeutic Alternatives
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- Redacted Negotiation Meeting Summaries for Xarelto
- Redacted Data Submitted by the Primary Manufacturer and Other Interested Parties for Xarelto

MFP Explanation Narrative for Xarelto

Summary of the Negotiation Process

CMS followed the negotiation process laid out in the IRA and in the revised guidance. On August 29, 2023, CMS announced the 10 selected drugs for the first cycle of negotiations, which included Xarelto. The Primary Manufacturers of the selected drugs signed agreements to participate in the Negotiation Program by the deadline in the IRA of October 1, 2023 and submitted information on the selected drugs by the deadline in the IRA of October 2, 2023.

CMS collected relevant data from numerous sources, such as written submissions from the Primary Manufacturers and other interested parties in response to an information collection request issued for the Negotiation Program (referred to as the “Negotiation Program information collection request” throughout this document), feedback from patient-focused listening sessions, meetings between CMS and the Primary Manufacturers to discuss the information submitted, and CMS’ literature review.⁴

Using the information collected, CMS then developed initial offers for the selected drugs, which were based on the factors outlined in the IRA for CMS’ determination of offers and which CMS developed in accordance with the process described in the revised guidance.⁵ As required by the IRA, CMS’ initial offers each included a concise justification on the range of evidence and other information within the negotiation factors that CMS found compelling during the development of the initial offer. The Primary Manufacturers each responded by declining CMS’ initial offer and providing a written counteroffer and justification for such offer, including considerations based on the negotiation factors.

³ The MFP is expressed as the price per 30-days equivalent supply. See section 60.1 of the [revised guidance](#) and the [Negotiated Prices for Initial Price Applicability Year 2026 Fact Sheet](#) for additional information.

⁴ The Negotiation Program information collection request is available on the Office of Management and Budget’s (OMB’s) website at the following link: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202306-0938-013.

⁵ Section 1194(e) of the Act requires CMS to consider certain data as the basis for all offers and counteroffers in the negotiation. These data, which are referred to in this document as the “negotiation factors,” are discussed in more detail later in this document. More information on the negotiation factors is also available in sections 50, 60.3 and 60.4 of the [revised guidance](#). CMS’ process for developing the initial offers is described in section 60.3 of the revised guidance.

CMS considered each counteroffer proposed by the Primary Manufacturers and declined each counteroffer. CMS and each Primary Manufacturer then held three negotiation meetings. These meetings included extensive discussion of the negotiation factors, including any new information consistent with the factors that may have become available about the selected drugs or therapeutic alternatives, CMS' initial offer and the Primary Manufacturer's written counteroffer, and, in some cases, additional proposals for an MFP.

Across the first cycle of negotiations for all ten selected drugs, more than 50 revised offers or counteroffers were proposed by CMS or a Primary Manufacturer, not including the ten initial offers CMS made and the ten written counteroffers provided by Primary Manufacturers. During the negotiation meetings, CMS revised its initial offer for each selected drug upwards at least once in response to the discussions with the Primary Manufacturer. While many of the details of the negotiations are confidential between CMS and each Primary Manufacturer, the frequency of revised offers and counteroffers in the first cycle of negotiations indicates the robustness of the negotiations that occurred for each of the ten drugs. CMS' approach to its negotiations with each Primary Manufacturer turned on the particular details relevant to each selected drug and was sensitive to the issues raised during the course of CMS' conversations with the Primary Manufacturer. CMS anticipates this drug-specific approach will continue to inform CMS' negotiations with participating manufacturers in future cycles of negotiation.

Overall, in six of ten negotiations CMS moved more than the Primary Manufacturer during the meetings and for the final offer (if applicable) prior to reaching agreement, and in four of ten negotiations the Primary Manufacturer moved more than CMS prior to reaching agreement. For five of the selected drugs, this process of exchanging revised offers and counteroffers resulted in CMS and the Primary Manufacturer reaching an agreement on a negotiated price for the selected drug in association with a negotiation meeting. In four of these cases, CMS accepted a revised counteroffer proposed by the Primary Manufacturer. For the remaining five selected drugs, CMS sent a written final offer to the Primary Manufacturer, consistent with the process described in the revised guidance, and in each instance, the Primary Manufacturer accepted CMS' offer on or before the statutory deadline. Throughout the negotiation process, CMS and the Primary Manufacturers exchanged perspectives about a range of topics related to the negotiation factors, and while the parties did not always agree, CMS appreciated the Primary Manufacturers' engagement.

A detailed timeline of the negotiation process for Xarelto is below.

- August 29, 2023: CMS announced the 10 selected drugs for initial price applicability year 2026
- October 1, 2023: Deadline for the Primary Manufacturer to sign an agreement to participate in the Negotiation Program
- October 2, 2023: Deadline for the Primary Manufacturer and the public to submit information related to Xarelto in response to the Negotiation Program information collection request
- October 25, 2023: CMS met with the Primary Manufacturer regarding its response to the Negotiation Program information collection request
- November 15, 2023: CMS held a patient-focused listening session for Xarelto
- February 1, 2024: CMS provided the Primary Manufacturer with CMS' initial offer
- March 1, 2024: The Primary Manufacturer rejected CMS' initial offer and provided CMS with a counteroffer
- March 29, 2024: CMS rejected the Primary Manufacturer's counteroffer and invited the Primary Manufacturer to a negotiation meeting
- May 1, 2024: CMS and the Primary Manufacturer met for the first negotiation meeting

- June 3, 2024: CMS and the Primary Manufacturer met for the second negotiation meeting
- June 24, 2024: CMS and the Primary Manufacturer met for the third negotiation meeting
- August 1, 2024: The negotiation period ended
- August 15, 2024: MFP of \$197.00 was published

Indications for Xarelto

Xarelto is an oral anticoagulant that blocks factor Xa, an enzyme involved in production of thrombin in the blood and in the formation of blood clots. In people who are at high risk for having a blood clot, such as patients with nonvalvular atrial fibrillation, or patients undergoing hip or knee surgery, anticoagulation treatment prevents blood clots that can cause a stroke, or blood clots that can develop in the legs or lungs.⁶

For Xarelto, CMS included the following indications in its assessment⁷:

Description of indication	Terminology used in this document
<ul style="list-style-type: none"> • To reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation. 	NVAF
<ul style="list-style-type: none"> • For the prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery. 	VTE prophylaxis following hip or knee surgery
<ul style="list-style-type: none"> • For the treatment of DVT. • For the treatment of pulmonary embolism (PE). • For the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months. • For treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment. 	The treatment and reduction of risk of VTE - related indications (which includes DVT and PE) in adult and pediatric populations, referred to as active and recurrent VTE

⁶ To compose this brief description, CMS used various sources, including MedlinePlus, a free online health information resource for patients and the general public. MedlinePlus is a service of the National Library of Medicine (NLM), a part of the U.S. National Institutes of Health (NIH). For more information about any drugs or conditions mentioned in this document, MedlinePlus can be accessed at: <https://medlineplus.gov/>.

⁷ CMS' process for identifying indications for a selected drug was to identify the FDA-approved indication(s) not otherwise excluded from coverage or otherwise restricted under section 1860D-2(e)(2) of the Act, using prescribing information approved by the FDA for the selected drug, in accordance with section 1194(e)(2)(B) of the Act. CMS considered off-label use when identifying indications if such use was included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia. CMS included indications that met these criteria during the negotiation period. Indications newly approved by FDA or included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia after the end of the negotiation period were not included.

Description of indication	Terminology used in this document
<ul style="list-style-type: none"> In combination with aspirin, to reduce the risk of major cardiovascular events in adult patients with coronary artery disease (CAD). 	CAD
<ul style="list-style-type: none"> In combination with aspirin, to reduce the risk of major thrombotic vascular events in adult patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization due to symptomatic PAD. 	PAD
<ul style="list-style-type: none"> For the prophylaxis of VTE and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other VTE risk factors and not at high risk of bleeding. 	VTE prophylaxis in the acutely ill
<ul style="list-style-type: none"> For thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease who have undergone the Fontan procedure. 	Post-Fontan procedure

Table 1. NVAf = nonvalvular atrial fibrillation. For purposes of CMS’ consideration of indications for Xarelto, CMS grouped certain indications using the terminology as shown in this table. CMS’ use of the terms listed here does not alter the FDA-approved indications for Xarelto.

Factors Applied

Consistent with the IRA, CMS considered certain negotiation factors as the basis for determining all offers and counteroffers during the negotiation process.

The following negotiation factors are referred to in this document as “manufacturer-specific data”⁸:

- Research and development (R&D) costs of the Primary Manufacturer for Xarelto and the extent to which the Primary Manufacturer has recouped R&D costs;
- Current unit costs of production and distribution of Xarelto;
- Prior Federal financial support for novel therapeutic discovery and development with respect to Xarelto;
- Data on pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals for New Drug Applications and Biologics License Applications for Xarelto;⁹ and
- Market data and revenue and sales volume data for Xarelto in the United States (U.S.).

⁸ These factors are listed at section 1194(e)(1) of the Act.

⁹ New Drug Applications are approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and Biologics License Applications are approved under section 351(a) of the Public Health Service Act.

The following negotiation factors are referred to in this document as “evidence about Xarelto and therapeutic alternatives to Xarelto”¹⁰:

- The extent to which Xarelto represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives;
- Prescribing information approved by the FDA for Xarelto and therapeutic alternatives to Xarelto;
- Comparative effectiveness of Xarelto and therapeutic alternatives to Xarelto, taking into consideration the effects of Xarelto and therapeutic alternatives to Xarelto on specific populations, such as individuals with disabilities, the elderly, the terminally ill, children, and other patient populations; and
- The extent to which Xarelto and therapeutic alternatives to Xarelto address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.

The below sections describe how CMS considered and applied these factors during the negotiation process. CMS considered these factors, taking into account all data in totality during the negotiation process.

CMS and the Primary Manufacturer did not always agree on the information presented below, and the Primary Manufacturer was not restricted to consideration of these factors during the negotiation process but was free to discuss any topics with CMS it deemed relevant to its consideration of offer(s) and counteroffer(s) for Xarelto.

Manufacturer-Specific Data

CMS considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data factors. These factors include R&D costs and the extent to which the Primary Manufacturer has recouped R&D costs, current unit costs of production and distribution, prior Federal financial support, data on pending and approved patents and exclusivities recognized by the FDA, and market data, including revenue and sales volume data for the drug in the United States. CMS considered these factors in totality, as part of its application of the negotiation factors during the negotiation process.

The Primary Manufacturer provided CMS with information for each of these factors in response to the Negotiation Program information collection request.¹¹ For R&D costs, CMS requested information separated into various categories of costs related to R&D, including acquisition costs, pre-clinical research costs, post-Investigational New Drug costs, costs of failed or abandoned products related to Xarelto, and other allowable direct costs. CMS also requested the global and U.S. total lifetime net revenue for Xarelto to provide insight into the extent to which the Primary Manufacturer has recouped R&D costs. CMS requested current average unit costs of production for Xarelto and current average unit costs of distribution for Xarelto separately, as well as a description of the methodology the Primary

¹⁰ These factors are listed at section 1194(e)(2) of the Act. In accordance with section 1194(e)(2) and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, non-disabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs).

¹¹ In accordance with the revised guidance, CMS treats R&D costs and the extent to which they are recouped, unit costs of production and distribution, pending patent applications, and market, revenue, and sales volume data as proprietary, unless the information that is provided to CMS is already publicly available. For more information, see section 40.2.1 of the [revised guidance](#).

Manufacturer used to estimate such costs. For information related to prior Federal financial support, CMS requested the total amount of Federal financial support received, as well as a breakdown by various types of financial support, like tax credits and National Institutes of Health funding. CMS requested information on patents, both expired and unexpired, issued by the U.S. Patent and Trademark Office, patent applications, regulatory exclusivity periods, and active and pending FDA applications and approvals. For market data, CMS requested information about the prices for Xarelto and volume dispensed for other payers in the U.S. market, including commercial payers (e.g., the U.S. commercial average net price), Medicaid (Medicaid Best Price), and other Federal payers (the Federal supply schedule price and the Big Four price).

Throughout the negotiation process, CMS holistically considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data negotiation factors for the purpose of negotiating an MFP for Xarelto. For example, CMS applied information on prices for Xarelto available to other payers in the U.S. market and how they compared to any offers or counteroffers when considering whether a potential price was consistent with CMS' aim to arrive at an agreement on the lowest possible MFP. The totality of CMS' application of these factors, in conjunction with application of the factors described below, informed CMS' negotiation of the MFP with the Primary Manufacturer.

Evidence about Xarelto and Therapeutic Alternatives to Xarelto

CMS considered information related to the negotiation factors regarding evidence about Xarelto and therapeutic alternatives to Xarelto. CMS' holistic consideration of clinical benefit included evidence from sources such as: pivotal clinical trials, pre-specified subgroup analyses, clinical practice guidelines, expert consensus statements, comparative clinical evidence, published literature reviews, real-world evidence, and FDA prescription drug labeling, among others. CMS evaluated the evidence based on a variety of considerations, including relevance and credibility, giving priority to well-designed and well-conducted studies, as stated in the revised guidance.¹² In general, CMS prioritized direct comparative evidence (e.g., head-to-head randomized controlled trials) when available. CMS also reviewed mixed and/or indirect treatment comparisons (e.g., network meta-analyses) when available and real-world evidence (e.g., observational studies) when available as part of its holistic assessment of comparative evidence.

In addition to information from the Primary Manufacturer, CMS received information from the public, including from patients during the patient-focused listening session held by CMS on November 15, 2023.¹³ Patient input was important to CMS' consideration of the evidence about Xarelto and therapeutic alternatives to Xarelto, including to help identify outcomes of interest for patients and to understand additional considerations such as treatment complexity. For example, some patients taking Xarelto described that they appreciated having an option that required minimal monitoring and minimal dietary restrictions. This was one consideration among the many that informed CMS' understanding of

¹² In section 50.2 of the [revised guidance](#), CMS stated, "When reviewing the literature from the public and manufacturer submissions as well as literature from CMS' review, CMS will consider the source, rigor of the study methodology, current relevance to the selected drug and its therapeutic alternative(s), whether the study has been through peer review, study limitations, degree of certainty of conclusions, risk of bias, study time horizons, generalizability, study population, and relevance to the negotiation factors listed in section 1194(e)(2) of the Act to ensure the integrity of the contributing data within the negotiation process. CMS will prioritize research, including both observational research and research based on randomized samples, that is methodologically rigorous, appropriately powered (i.e., has sufficient sample size) to answer the primary question of the research, and structured to avoid potential false positive findings due to multiple subgroup analyses."

¹³ The redacted transcript for this patient-focused listening session is available at the following link: <https://www.cms.gov/files/document/xarelto-transcript-111523.pdf>.

the factors regarding evidence about Xarelto and its therapeutic alternatives. Throughout all of the patient-focused listening sessions for the first cycle of negotiations, speakers provided insight on the importance of affordability and access, which provided CMS helpful context for the speakers’ described experiences.

Therapeutic Alternatives

The IRA directs CMS to compare Xarelto to therapeutic alternatives in its determination of offers and consideration of counteroffers for Xarelto.¹⁴ In the revised guidance, CMS defines a therapeutic alternative for the first cycle of negotiations as a pharmaceutical product that is clinically comparable to the selected drug.¹⁵

Importantly, use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are interchangeable or otherwise universally appropriate to prescribe for an individual in place of Xarelto or that these are the only pharmaceutical treatments that might be used by a person with one of the indications treated by Xarelto. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient’s needs based on the patient’s health, history, experience, and preferences, the provider’s expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

During the negotiation process, CMS identified therapeutic alternatives to Xarelto based on a holistic consideration of the available evidence from a range of sources. In addition to the sources listed above, such as data submitted by the Primary Manufacturer and the public and widely accepted clinical guidelines, other examples of data sources used include the following: drug classification systems commonly used in the public and commercial sector for formulary development, indications included in CMS-approved Part D compendia, and drug or drug class reviews.

The following table lists the therapeutic alternatives, among all clinically comparable alternatives that CMS reviewed, which were particularly relevant to CMS’ consideration, due to guideline recommendations, utilization in the Medicare population, and other considerations.

Indication	Therapeutic Alternatives
NVAF	<ul style="list-style-type: none"> • Apixaban • Dabigatran
VTE prophylaxis following hip or knee surgery	<ul style="list-style-type: none"> • Apixaban • Dabigatran
Active and recurrent VTE	<ul style="list-style-type: none"> • Apixaban • Dabigatran
CAD	<ul style="list-style-type: none"> • Ticagrelor
PAD	<ul style="list-style-type: none"> • Clopidogrel
VTE prophylaxis in the acutely ill	<ul style="list-style-type: none"> • Enoxaparin
Post-Fontan procedure	<ul style="list-style-type: none"> • Warfarin

Table 2. CAD = coronary artery disease; NVAF = nonvalvular atrial fibrillation; PAD = peripheral artery disease VTE = venous thromboembolism. Use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are

¹⁴ See section 1194(e)(2) of the Act and sections 50, 60.3 and 60.4 of the [revised guidance](#) for additional information.

¹⁵ This definition appears in Appendix C of the [revised guidance](#).

interchangeable or otherwise universally appropriate to prescribe for an individual in place of Xarelto or that these are the only pharmaceutical treatments that might be used by a person with one of the indications treated by Xarelto. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient’s needs based on the patient’s health, history, experience, and preferences, the provider’s expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

CMS considered utilization for Xarelto and its therapeutic alternatives by indication as one part of its application of the negotiation factors.

Outcomes and Additional Considerations

Outcomes are measurable effects or impacts of a treatment or intervention. Outcomes can be used to measure differences in the safety or effectiveness of different treatments. Patient-centered outcomes are outcomes identified by patients that are important to how they feel, function, or survive. To consider comparative effectiveness between Xarelto and therapeutic alternatives to Xarelto, CMS identified clinically relevant and patient-centered outcomes of interest from the body of available literature to evaluate for each indication of Xarelto. CMS then identified evidence comparing Xarelto to therapeutic alternatives based on these outcomes. The following table includes a non-exhaustive list of outcomes that were of interest to CMS in its consideration of Xarelto:

Indication	Effectiveness Outcomes	Safety Outcomes
NVAF	<ul style="list-style-type: none"> Prevention of stroke and systemic embolism 	<ul style="list-style-type: none"> Bleeding
VTE prophylaxis following hip or knee surgery	<ul style="list-style-type: none"> VTE 	<ul style="list-style-type: none"> Bleeding
Active and recurrent VTE	<ul style="list-style-type: none"> VTE 	<ul style="list-style-type: none"> Bleeding
CAD	<ul style="list-style-type: none"> MACE 	<ul style="list-style-type: none"> Bleeding
PAD	<ul style="list-style-type: none"> MACE MALE 	<ul style="list-style-type: none"> Bleeding
VTE prophylaxis in the acutely ill	<ul style="list-style-type: none"> VTE 	<ul style="list-style-type: none"> Bleeding
Post-Fontan procedure	<ul style="list-style-type: none"> Stroke VTE Intra-cardiac thrombus 	<ul style="list-style-type: none"> Bleeding

Table 3. CAD = coronary artery disease; MACE = major adverse cardiac events; MALE = major adverse limb events. NVAF = nonvalvular atrial fibrillation; PAD = peripheral artery disease; VTE = venous thromboembolism. Outcomes identified in this table were of interest to CMS in its evaluation of Xarelto. Evidence to support an assessment may not have been available for every outcome of interest.

Outcomes, like those listed above, were identified as being of interest to CMS based on their importance to patients and their ability to measure how effective and safe a drug is when used to treat these indications. For example, prevention of strokes, or blood clots in the legs or lungs, are key outcomes that are often used to evaluate the effectiveness of treatments for these indications. In addition, the risk of bleeding is an outcome that reflects important safety considerations when evaluating drugs for these indications.

Additionally, CMS considered the extent to which Xarelto represents a therapeutic advance as compared to existing therapeutic alternatives, and the extent to which Xarelto and its therapeutic alternatives address an unmet medical need. CMS also evaluated access, equity, and health outcomes for specific

populations (including individuals with disabilities, the elderly, individuals who are terminally ill, children, and other patient populations).

For the purpose of negotiating the MFP for Xarelto, CMS holistically considered the negotiation factors regarding evidence about Xarelto and its therapeutic alternatives, including consideration of the clinical benefit of Xarelto in the context of its therapeutic alternatives. For example, CMS applied its understanding of the comparative effectiveness of Xarelto and its therapeutic alternatives by assessing prevention of blood clots and rates of bleeding for each of the identified indications when negotiating with the Primary Manufacturer. CMS' holistic assessment was also informed by additional contextual considerations, such as route of administration, use in patients with end-stage renal disease or on dialysis, patients with obesity, patients with cancer, pediatric patients and the elderly.

Throughout the negotiation process, including the development of the initial offer and in the consideration of any offers and counteroffers, CMS applied these and other factors regarding evidence about Xarelto and therapeutic alternatives. The totality of CMS' application of these factors, in conjunction with application of the manufacturer-submitted data negotiation factors described above, informed CMS' negotiation of the MFP with the Primary Manufacturer.

Citations to Data Reviewed during the Negotiation Process for Xarelto

CMS provides below a list of citations representative of evidence that CMS reviewed during the negotiation process, including citations provided by the Primary Manufacturer and the public in response to the Negotiation Program information collection request, those included in CMS' initial offer concise justification, and other citations which were considered during the evaluation of the Primary Manufacturer's counteroffer and during negotiation meetings.

Consistent with the IRA and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs). Inclusion on this list of a citation that contains such evidence does not mean that CMS used such evidence in the course of the negotiation.

This list is intended to provide insight into the range of evidence that various parties, including CMS and the Primary Manufacturer, identified as being relevant to the negotiation. This list does not represent the totality of evidence that CMS reviewed and considered as part of its holistic consideration of the negotiation factors in the determination of any offers and consideration of any counteroffers.

1. About atrial fibrillation [Internet]. U.S. Centers for Disease Control and Prevention [cited 2023 Jun 26]. Available from: https://www.cdc.gov/heart-disease/about/atrial-fibrillation.html?CDC_AAref_Val=https://www.cdc.gov/heartdisease/atrial_fibrillation.htm.
2. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. *Gastroenterology*. 2017;152(5):1014-22 e1. Epub 20161230. doi: 10.1053/j.gastro.2016.12.018. PubMed PMID: 28043907.
3. Adeboyeje G, Sylwestrzak G, Barron JJ, White J, Rosenberg A, Abarca J, et al. Major Bleeding Risk During Anticoagulation with Warfarin, Dabigatran, Apixaban, or Rivaroxaban in Patients with Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm*. 2017;23(9):968-78. doi: 10.18553/jmcp.2017.23.9.968. PubMed PMID: 28854073; PubMed Central PMCID: PMC10398327.
4. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. Epub 20130701. doi: 10.1056/NEJMoa1302507. PubMed PMID: 23808982.
5. Akintoye E, Miranda WR, Veldtman GR, Connolly HM, Egbe AC. National trends in Fontan operation and in-hospital outcomes in the USA. *Heart*. 2019;105(9):708-14. Epub 20181030. doi: 10.1136/heartjnl-2018-313680. PubMed PMID: 30377261.
6. Alberts M, Chen YW, Lin JH, Kogan E, Twyman K, Milentijevic D. Risks of Stroke and Mortality in Atrial Fibrillation Patients Treated With Rivaroxaban and Warfarin. *Stroke*. 2020;51(2):549-55. Epub 20191231. doi: 10.1161/strokeaha.119.025554. PubMed PMID: 31888412; PubMed Central PMCID: PMC7004448.
7. Alberts MJ, Peacock WF, Fields LE, Bunz TJ, Nguyen E, Milentijevic D, et al. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. *Int J Cardiol*. 2016;215:11-3. Epub 20160404. doi: 10.1016/j.ijcard.2016.03.212. PubMed PMID: 27104919.

8. Alsaied T, Possner M, Eynde JVd, Kreutzer J. Anticoagulation Algorithm For Fontan Patients. American College of Cardiology; 2023 Apr 5. Available from: <https://www.acc.org/Latest-in-Cardiology/Articles/2023/04/05/14/10/Anticoagulation-Algorithm-For-Fontan-Patients>.
9. Ambler GK, Nordanstig J, Behrendt CA, Twine CP. Network Meta-analysis of the Benefit of Aspirin with Rivaroxaban vs. Clopidogrel for Patients with Stable Symptomatic Lower Extremity Arterial Disease. *Eur J Vasc Endovasc Surg.* 2021;62(4):654-5. Epub 20210825. doi: 10.1016/j.ejvs.2021.05.038. PubMed PMID: 34452837.
10. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S144-S74. doi: 10.2337/dc22-S010. PubMed PMID: 34964815.
11. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022 Jan 1;45(Suppl 1):S144-S174. doi: 10.2337/dc22-S010. Erratum in: *Diabetes Care.* 2022 May 1;45(5):1296. doi: 10.2337/dc22-er05. Erratum in: *Diabetes Care.* 2022 Sep 01;45(9):2178-2181. doi: 10.2337/dc22-ad08. PubMed PMID: 34964815.
12. Amin A, Garcia Reeves AB, Li X, Dhamane A, Luo X, Di Fusco M, et al. Effectiveness and safety of oral anticoagulants in older adults with non-valvular atrial fibrillation and heart failure. *PLoS One.* 2019;14(3):e0213614. Epub 20190325. doi: 10.1371/journal.pone.0213614. PubMed PMID: 30908512; PubMed Central PMCID: PMC6433218.
13. Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, et al. A Real-World Observational Study of Hospitalization and Health Care Costs Among Nonvalvular Atrial Fibrillation Patients Prescribed Oral Anticoagulants in the U.S. Medicare Population. *J Manag Care Spec Pharm.* 2018;24(9):911-20. doi: 10.18553/jmcp.2018.24.9.911. PubMed PMID: 30156450; PubMed Central PMCID: PMC10398085.
14. Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, et al. A Real-World Observational Study of Hospitalization and Health Care Costs Among Nonvalvular Atrial Fibrillation Patients Prescribed Oral Anticoagulants in the U.S. Medicare Population. *J Manag Care Spec Pharm.* 2020;26(5):639-51. doi: 10.18553/jmcp.2020.26.5.639. PubMed PMID: 32347184; PubMed Central PMCID: PMC10398709.
15. Amputation Reduction and Compassion Act of 2023, H.R. 4261, 118th Congress. (2023).
16. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. *J Am Coll Cardiol.* 2018;71(20):2306-15. Epub 20180311. doi: 10.1016/j.jacc.2018.03.008. PubMed PMID: 29540326.
17. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv.* 2019;3(23):3898-944. doi: 10.1182/bloodadvances.2019000975. PubMed PMID: 31794602; PubMed Central PMCID: PMC6963238.
18. Andersson NW, Svanstrom H, Lund M, Pasternak B, Melbye M. Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation. *Int J Cardiol.* 2018;268:113-9. Epub 20180620. doi: 10.1016/j.ijcard.2018.03.047. PubMed PMID: 29934230.
19. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the

- Management of Atrial Fibrillation. *Can J Cardiol.* 2020;36(12):1847-948. Epub 20201022. doi: 10.1016/j.cjca.2020.09.001. PubMed PMID: 33191198.
20. Aryal MR, Gosain R, Donato A, Yu H, Katel A, Bhandari Y, et al. Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. *Blood Adv.* 2019;3(15):2381-7. doi: 10.1182/bloodadvances.2019000572. PubMed PMID: 31405948; PubMed Central PMCID: PMC6693001.
 21. Aslan O, Yildirim S. Rivaroxaban and apixaban in patients with atrial fibrillation; a real-world data. *Turk J Med Sci.* 2022;52(4):948-57. Epub 20220810. doi: 10.55730/1300-0144.5395. PubMed PMID: 36326404; PubMed Central PMCID: PMC10387864.
 22. Atrial fibrillation: diagnosis and management. National Institute for Health and Care Excellence; 2021 Apr 27. Report No. NG196. Available from: <https://www.nice.org.uk/guidance/ng196>.
 23. Baker WL, Roberts MS, Bessada Y, Caroti KS, Ashton V, Bookhart BK, et al. Comparative outcomes associated with rivaroxaban versus warfarin use in elderly patients with atrial fibrillation or acute venous thromboembolism managed in the United States: a systematic review of observational studies. *Curr Med Res Opin.* 2023;39(9):1183-94. Epub 20230824. doi: 10.1080/03007995.2023.2247988. PubMed PMID: 37584187.
 24. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and Risk of Amputation in Patients With Diabetes Mellitus and Peripheral Artery Disease. *Arterioscler Thromb Vasc Biol.* 2020;40(8):1808-17. Epub 20200625. doi: 10.1161/atvbaha.120.314595. PubMed PMID: 32580632; PubMed Central PMCID: PMC7377955.
 25. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-510. Epub 20101203. doi: 10.1056/NEJMoa1007903. PubMed PMID: 21128814.
 26. Berger A, Simpson A, Bhagnani T, Leeper NJ, Murphy B, Nordstrom B, et al. Incidence and Cost of Major Adverse Cardiovascular Events and Major Adverse Limb Events in Patients With Chronic Coronary Artery Disease or Peripheral Artery Disease. *Am J Cardiol.* 2019;123(12):1893-9. Epub 20190316. doi: 10.1016/j.amjcard.2019.03.022. PubMed PMID: 31014542.
 27. Beyer-Westendorf J, Lensing AW, Arya R, Bounameaux H, Cohen AT, Wells PS, et al. Choosing wisely: The impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials. *Thromb Res.* 2017;149:29-37. Epub 20161121. doi: 10.1016/j.thromres.2016.11.014. PubMed PMID: 27886530.
 28. Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, et al. Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes Mellitus and Cardiovascular Disease: Insights From the COMPASS Trial. *Circulation.* 2020;141(23):1841-54. Epub 20200328. doi: 10.1161/circulationaha.120.046448. PubMed PMID: 32223318; PubMed Central PMCID: PMC7314494.
 29. Boehringer Ingelheim Pharmaceuticals, Inc. Pradaxa (dabigatran etexilate) [package insert]. U.S. Food and Drug Administration. Revised 2021 Jun. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214358s000lbl.pdf.
 30. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. *N Engl J Med.* 2020;382(21):1994-2004. Epub 20200328. doi: 10.1056/NEJMoa2000052. PubMed PMID: 32222135.

31. Bonde AN, Martinussen T, Lee CJ, Lip GYH, Staerk L, Bang CN, et al. Rivaroxaban Versus Apixaban for Stroke Prevention in Atrial Fibrillation: An Instrumental Variable Analysis of a Nationwide Cohort. *Circ Cardiovasc Qual Outcomes*. 2020;13(4):e006058. Epub 20200414. doi: 10.1161/CIRCOUTCOMES.119.006058. PubMed PMID: 32283966.
32. Briasoulis A, Mentias A, Mazur A, Alvarez P, Leira EC, Vaughan Sarrazin MS. Comparative Effectiveness and Safety of Direct Oral Anticoagulants in Obese Patients with Atrial Fibrillation. *Cardiovasc Drugs Ther*. 2021;35(2):261-72. Epub 20210106. doi: 10.1007/s10557-020-07126-2. PubMed PMID: 33404923; PubMed Central PMCID: PMC8382577.
33. Bristol-Myers Squibb. Coumadin (warfarin sodium) [package insert]. U.S. Food and Drug Administration. 2010 Jan. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf.
34. Bristol-Myers Squibb. Eliquis (apixaban) [package insert]. U.S. Food and Drug Administration. 2021 Apr. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202155s032lbl.pdf.
35. Bruno XJ, Koh I, Lutsey PL, Walker RF, Roetker NS, Wilkinson K, et al. Venous thrombosis risk during and after medical and surgical hospitalizations: The medical inpatient thrombosis and hemostasis (MITH) study. *J Thromb Haemost*. 2022;20(7):1645-52. Epub 20220427. doi: 10.1111/jth.15729. PubMed PMID: 35426248; PubMed Central PMCID: PMC9247009.
36. Buckner TW, Key NS. Venous thrombosis in blacks. *Circulation*. 2012;125(6):837-9. doi: 10.1161/CIRCULATIONAHA.111.073098. PubMed PMID: 22331921.
37. Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-97. Epub 20120326. doi: 10.1056/NEJMoa1113572. PubMed PMID: 22449293.
38. Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, et al. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med*. 2008;168(9):928-35. doi: 10.1001/archinte.168.9.928. PubMed PMID: 18474756; PubMed Central PMCID: PMC2931579.
39. Burnett AE, Barnes GD, Allen AL, Ansell J, Blumenstein M, Connors JM, et al. Comment on: 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(12):3951-3. Epub 20230913. doi: 10.1111/jgs.18579. PubMed PMID: 37702478.
40. Bytzer P, Connolly SJ, Yang S, Ezekowitz M, Formella S, Reilly PA, et al. Analysis of upper gastrointestinal adverse events among patients given dabigatran in the RE-LY trial. *Clin Gastroenterol Hepatol*. 2013;11(3):246-52 e1-5. Epub 20121024. doi: 10.1016/j.cgh.2012.10.021. PubMed PMID: 23103906.
41. Camm AJ, Fox KAA, Peterson E. Challenges in comparing the non-vitamin K antagonist oral anticoagulants for atrial fibrillation-related stroke prevention. *Europace*. 2018;20(1):1-11. doi: 10.1093/europace/eux086. PubMed PMID: 29040518.
42. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, et al. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. *Circulation*. 2022;145(4):242-55. Epub 20220105. doi: 10.1161/circulationaha.121.056355. PubMed PMID: 34985309; PubMed Central PMCID: PMC8800560.

43. CDC WONDER: About Underlying Cause of Death, 1999-2020 [Internet]. Georgia: U.S. Centers for Disease Control and Prevention [cited 2023 Oct 2]. Available from: <https://wonder.cdc.gov/ucd-icd10.html>.
44. Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research. Benefit-Risk Assessment for New Drug and Biological Products. U.S. Food and Drug Administration; 2023 Oct. Docket No. FDA-2020-D-2316. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products>.
45. Center for Drug Evaluation & Research (CDER). Intracranial hemorrhage following direct oral anticoagulant use: An inverse probability of treatment weighting analysis. Sentinel; 2022 Apr 25. Available from: <https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/thromboembolic-stroke-major-extracranial-bleeding-0>.
46. Center for Drug Evaluation & Research (CDER). Stroke, intracranial hemorrhage, and bleeding following dabigatran, rivaroxaban, and apixaban use in patients aged 65 or older: a propensity score matched analysis. Sentinel; 2020 Sep 14. Available from: <https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/stroke-intracranial-hemorrhage-and-bleeding-following>.
47. Chan YH, Chao TF, Chen SW, Lee HF, Chen WM, Li PR, et al. Development of Interstitial Lung Disease Among Patients With Atrial Fibrillation Receiving Oral Anticoagulants in Taiwan. *JAMA Netw Open*. 2022;5(11):e2243307. Epub 20221101. doi: 10.1001/jamanetworkopen.2022.43307. PubMed PMID: 36413365; PubMed Central PMCID: PMC9682427.
48. Chowdhury KR, Michaud J, Yu OHY, Yin H, Azoulay L, Renoux C. Effectiveness and Safety of Apixaban versus Rivaroxaban in Patients with Atrial Fibrillation and Type 2 Diabetes Mellitus. *Thromb Haemost*. 2022;122(10):1794-803. Epub 20220315. doi: 10.1055/a-1798-2116. PubMed PMID: 35292949.
49. Chronic Kidney Disease in the United States, 2023. Georgia: U.S. Centers for Disease Control and Prevention; 2023. Available From: <https://web.archive.org/web/20240217174631/https://www.cdc.gov/kidneydisease/pdf/CKD-Factsheet-H.pdf>.
50. Chugh Y, Gupta K, Krishna HB, Ayala RQ, Zepeda I, Grushko M, Faillace RT. Safety and efficacy of apixaban, dabigatran and rivaroxaban in obese and morbidly obese patients with heart failure and atrial fibrillation: A real-world analysis. *Pacing Clin Electrophysiol*. 2023;46(1):50-8. Epub 20221201. doi: 10.1111/pace.14623. PubMed PMID: 36419246.
51. Cohen AT, Berger SE, Milenkovic D, Hill NR, Lister S. Anticoagulant selection for patients with VTE-Evidence from a systematic literature review of network meta-analyses. *Pharmacol Res*. 2019;143:166-77. Epub 20190321. doi: 10.1016/j.phrs.2019.03.017. PubMed PMID: 30905806.
52. Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(6):513-23. doi: 10.1056/NEJMoa1111096. PubMed PMID: 23388003.
53. Cohen AT, Spiro TE, Spyropoulos AC, Committee MS. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(20):1945-6. doi: 10.1056/NEJMc1303641. PubMed PMID: 23675665.

54. Coleman C, Yuan Z, Schein J, Crivera C, Ashton V, Laliberté F, et al. Abstract 015: Importance of Balanced Follow-up Time and Other Study Design Considerations When Evaluating Adherence Using Two Novel Oral Anticoagulants. *Circulation: Cardiovascular Quality and Outcomes*. 2017;10(suppl_3):A015-A. doi: 10.1161/circoutcomes.10.suppl_3.015.
55. Coleman CI, Fermann GJ, Weeda ER, Wells PS, Ashton V, Crivera C, et al. Is Rivaroxaban Associated With Shorter Hospital Stays and Reduced Costs Versus Parenteral Bridging to Warfarin Among Patients With Pulmonary Embolism? *Clin Appl Thromb Hemost*. 2017;23(7):830-7. Epub 20160801. doi: 10.1177/1076029616661415. PubMed PMID: 27481875.
56. Coleman CI, Kharat AA, Bookhart B, Baker WL. Combination anticoagulant or P2Y12 inhibitor with low-dose aspirin versus low-dose aspirin alone in patients at risk or with documented coronary and/or peripheral artery disease. *Curr Med Res Opin*. 2022;38(1):27-34. Epub 20211026. doi: 10.1080/03007995.2021.1991294. PubMed PMID: 34641745.
57. Coleman CI, Thompson S, Ashton V, Palladino M, Bunz TJ. Rivaroxaban Versus Warfarin in African American Patients with Nonvalvular Atrial Fibrillation. *J Natl Med Assoc*. 2020;112(4):395-401. Epub 20200531. doi: 10.1016/j.jnma.2020.04.014. PubMed PMID: 32493618.
58. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanus F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):205-18. Epub 20171110. doi: 10.1016/s0140-6736(17)32458-3. PubMed PMID: 29132879.
59. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51. Epub 20090830. doi: 10.1056/NEJMoa0905561. PubMed PMID: 19717844.
60. Conti A, Renzi N, Catarzi S, Mazzucchelli M, Covelli A, Pampana A, et al. Bleeding Events in Patients 75 Years of Age and Older Under Long-term Anticoagulant Therapy: A Real-life Study. *Crit Pathw Cardiol*. 2020;19(3):131-8. doi: 10.1097/HPC.000000000000205. PubMed PMID: 32265352.
61. Cools F, Johnson D, Camm AJ, Bassand JP, Verheugt FWA, Yang S, et al. Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: Results from the GARFIELD-AF Registry. *J Thromb Haemost*. 2021;19(9):2322-34. Epub 20210723. doi: 10.1111/jth.15415. PubMed PMID: 34060704; PubMed Central PMCID: PMC8390436.
62. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. doi: 10.1093/eurheartj/ehz486. PubMed PMID: 31497854.
63. Costa OS, Thompson S, Ashton V, Palladino M, Bunz TJ, Coleman CI. Rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism in African American patients: a retrospective cohort analysis. *Thromb J*. 2020;18:6. Epub 20200408. doi: 10.1186/s12959-020-00219-w. PubMed PMID: 32292291; PubMed Central PMCID: PMC7140368.
64. Creager MA, Matsushita K, Arya S, Beckman JA, Duval S, Goodney PP, et al. Reducing Nontraumatic Lower-Extremity Amputations by 20% by 2030: Time to Get to Our Feet: A

- Policy Statement From the American Heart Association. *Circulation*. 2021;143(17):e875-e91. Epub 20210325. doi: 10.1161/CIR.0000000000000967. PubMed PMID: 33761757.
65. Dagenais GR, Dyal L, Bosch JJ, Leong DP, Aboyans V, Berkowitz SD, et al. Cardiovascular consequences of discontinuing low-dose rivaroxaban in people with chronic coronary or peripheral artery disease. *Heart*. 2021;107(14):1130-7. Epub 20210521. doi: 10.1136/heartjnl-2020-318758. PubMed PMID: 34021038; PubMed Central PMCID: PMC8257559.
 66. Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. *Lancet Haematol*. 2019;6(1):e20-e8. Epub 20181214. doi: 10.1016/S2352-3026(18)30191-1. PubMed PMID: 30558988.
 67. Dawwas GK, Cuker A, Barnes GD, Lewis JD, Hennessy S. Apixaban Versus Rivaroxaban in Patients With Atrial Fibrillation and Valvular Heart Disease : A Population-Based Study. *Ann Intern Med*. 2022;175(11):1506-14. Epub 20221018. doi: 10.7326/M22-0318. PubMed PMID: 36252244; PubMed Central PMCID: PMC10878325.
 68. Dawwas GK, Cuker A, Connors JM, Barnes GD. Apixaban has superior effectiveness and safety compared to rivaroxaban in patients with commercial healthcare coverage: A population-based analysis in response to CVS 2022 formulary changes. *Am J Hematol*. 2022;97(5):E173-E6. Epub 20220224. doi: 10.1002/ajh.26494. PubMed PMID: 35147235; PubMed Central PMCID: PMC8986609.
 69. Dawwas GK, Leonard CE, Lewis JD, Cuker A. Risk for Recurrent Venous Thromboembolism and Bleeding With Apixaban Compared With Rivaroxaban: An Analysis of Real-World Data. *Ann Intern Med*. 2022;175(1):20-8. Epub 20211207. doi: 10.7326/M21-0717. PubMed PMID: 34871048.
 70. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. *J Am Soc Nephrol*. 2020;31(1):186-96. Epub 20191108. doi: 10.1681/asn.2019060579. PubMed PMID: 31704740; PubMed Central PMCID: PMC6935010.
 71. De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and Efficacy of Vitamin K Antagonists versus Rivaroxaban in Hemodialysis Patients with Atrial Fibrillation: A Multicenter Randomized Controlled Trial. *J Am Soc Nephrol*. 2021;32(6):1474-83. Epub 20210322. doi: 10.1681/asn.2020111566. PubMed PMID: 33753537; PubMed Central PMCID: PMC8259651.
 72. Deitelzweig S, Baker CL, Dhamane AD, Mardekian J, Dina O, Rosenblatt L, et al. Comparison of readmissions among hospitalized nonvalvular atrial fibrillation patients treated with oral anticoagulants in the United States. *J Drug Assess*. 2020;9(1):87-96. Epub 20200424. doi: 10.1080/21556660.2020.1750418. PubMed PMID: 32489717; PubMed Central PMCID: PMC7241468.
 73. Deitelzweig S, Bruno A, Trocio J, Tate N, Gupta K, Lin J, Lingohr-Smith M. An early evaluation of bleeding-related hospital readmissions among hospitalized patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants. *Curr Med Res Opin*. 2016;32(3):573-82. Epub 20160101. doi: 10.1185/03007995.2015.1131676. PubMed PMID: 26652179.
 74. Deitelzweig S, Keshishian A, Kang A, Dhamane AD, Luo X, Klem C, et al. Use of Non-Vitamin K Antagonist Oral Anticoagulants Among Patients with Nonvalvular Atrial Fibrillation and

- Multimorbidity. *Adv Ther.* 2021;38(6):3166-84. Epub 20210507. doi: 10.1007/s12325-021-01724-8. PubMed PMID: 33963511; PubMed Central PMCID: PMC8190022.
75. Deitelzweig S, Keshishian A, Kang A, Dhamane AD, Luo X, Li X, et al. Effectiveness and Safety of Oral Anticoagulants among NVAF Patients with Obesity: Insights from the ARISTOPHANES Study. *J Clin Med.* 2020;9(6). Epub 20200528. doi: 10.3390/jcm9061633. PubMed PMID: 32481607; PubMed Central PMCID: PMC7355744.
 76. Deitelzweig S, Keshishian A, Kang A, Jenkins A, Atreja N, Schuler P, et al. Delaying clinical events among patients with non-valvular atrial fibrillation treated with oral anticoagulants: Insights from the ARISTOPHANES study. *Eur J Intern Med.* 2023;108:37-42. Epub 20221128. doi: 10.1016/j.ejim.2022.10.021. PubMed PMID: 36456387.
 77. Deitelzweig S, Keshishian A, Li X, Kang A, Dhamane AD, Luo X, et al. Comparisons between Oral Anticoagulants among Older Nonvalvular Atrial Fibrillation Patients. *J Am Geriatr Soc.* 2019;67(8):1662-71. Epub 20190521. doi: 10.1111/jgs.15956. PubMed PMID: 31112292; PubMed Central PMCID: PMC6852415.
 78. Deitelzweig S, Keshishian AV, Zhang Y, Kang A, Dhamane AD, Luo X, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients With Active Cancer. *JACC CardioOncol.* 2021;3(3):411-24. Epub 20210921. doi: 10.1016/j.jacc.2021.06.004. PubMed PMID: 34604802; PubMed Central PMCID: PMC8463723.
 79. Deitelzweig S, Luo X, Gupta K, Trocio J, Mardekian J, Curtice T, et al. Comparison of effectiveness and safety of treatment with apixaban vs. other oral anticoagulants among elderly nonvalvular atrial fibrillation patients. *Curr Med Res Opin.* 2017;33(10):1745-54. Epub 20170829. doi: 10.1080/03007995.2017.1334638. PubMed PMID: 28849676.
 80. Dhamane AD, Ferri M, Keshishian A, Russ C, Atreja N, Gutierrez C, et al. Effectiveness and Safety of Direct Oral Anticoagulants Among Patients with Non-valvular Atrial Fibrillation and Multimorbidity. *Adv Ther.* 2023;40(3):887-902. Epub 20221217. doi: 10.1007/s12325-022-02387-9. PubMed PMID: 36527598; PubMed Central PMCID: PMC9988801.
 81. Division for Heart Disease and Stroke Prevention. Atrial Fibrillation [Internet]. Georgia: U.S. Centers for Disease Control and Prevention; 2022 Oct 14 [cited 2023 Jun 26]. Available from: https://web.archive.org/web/20230526211654/https://www.cdc.gov/heartdisease/atrial_fibrillation.htm.
 82. Durand M, Schnitzer ME, Pang M, Carney G, Eltonsy S, Filion KB, et al. Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: A multi-database cohort study with meta-analysis. *Br J Clin Pharmacol.* 2021;87(6):2589-601. Epub 20201216. doi: 10.1111/bcp.14669. PubMed PMID: 33242339.
 83. Eck RJ, Elling T, Sutton AJ, Wetterslev J, Gluud C, van der Horst ICC, et al. Anticoagulants for thrombosis prophylaxis in acutely ill patients admitted to hospital: systematic review and network meta-analysis. *BMJ.* 2022;378:e070022. Epub 20220704. doi: 10.1136/bmj-2022-070022. PubMed PMID: 35788047; PubMed Central PMCID: PMC9251634.
 84. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med.* 2017;377(14):1319-30. Epub 20170827. doi: 10.1056/NEJMoa1709118. PubMed PMID: 28844192.
 85. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-510. Epub 20101203. doi: 10.1056/NEJMoa1007903. PubMed PMID: 21128814.

86. EINSTEIN-PE Investigators, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-97. Epub 20120326. doi: 10.1056/NEJMoa1113572. PubMed PMID: 22449293.
87. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Erratum. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes-2023. *Diabetes Care* 2023;46(Suppl. 1):S158-S190. *Diabetes Care*. 2023;46(4):898. doi: 10.2337/dc23-er04. PubMed PMID: 36700978; PubMed Central PMCID: PMC10090895.
88. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S158-S90. doi: 10.2337/dc23-S010. PubMed PMID: 36507632; PubMed Central PMCID: PMC9810475.
89. Errata to: *CHEST* 2021;160(6):2247-2259 and *CHEST* 2021;160(6):e545-e608. *Chest*. 2022;162(1):269. doi: 10.1016/j.chest.2022.05.028. PubMed PMID: 35809930.
90. Essien UR, Chiswell K, Kaltenbach LA, Wang TY, Fonarow GC, Thomas KL, et al. Association of Race and Ethnicity With Oral Anticoagulation and Associated Outcomes in Patients With Atrial Fibrillation: Findings From the Get With The Guidelines-Atrial Fibrillation Registry. *JAMA Cardiol*. 2022;7(12):1207-17. doi: 10.1001/jamacardio.2022.3704. PubMed PMID: 36287545; PubMed Central PMCID: PMC9608025.
91. Fadah K, Hechanova A, Mukherjee D. Epidemiology, Pathophysiology, and Management of Coronary Artery Disease in the Elderly. *Int J Angiol*. 2022;31(4):244-50. Epub 20220825. doi: 10.1055/s-0042-1751234. PubMed PMID: 36588871; PubMed Central PMCID: PMC9803549.
92. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e278S-e325S. doi: 10.1378/chest.11-2404. PubMed PMID: 22315265; PubMed Central PMCID: PMC3278063.
93. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126(25):e354-471. Epub 20121119. doi: 10.1161/CIR.0b013e318277d6a0. PubMed PMID: 23166211.
94. Fontan procedure [Internet]. Ohio: Cleveland Clinic; 2022 Dec 19 [cited 2023 Oct 2]. Available from: <https://my.clevelandclinic.org/health/treatments/24545-fontan-procedure>.
95. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF. *Circulation*. 2016;134(1):37-47. doi: 10.1161/circulationaha.116.021890. PubMed PMID: 27358435.
96. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-

- valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32(19):2387-94. Epub 20110828. doi: 10.1093/eurheartj/ehr342. PubMed PMID: 21873708.
97. Fox KAA, Eikelboom JW, Shestakovska O, Connolly SJ, Metsarinne KP, Yusuf S. Rivaroxaban Plus Aspirin in Patients With Vascular Disease and Renal Dysfunction: From the COMPASS Trial. *J Am Coll Cardiol*. 2019;73(18):2243-50. doi: 10.1016/j.jacc.2019.02.048. PubMed PMID: 31072566.
 98. Fralick M, Colacci M, Schneeweiss S, Huybrechts KF, Lin KJ, Gagne JJ. Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice: A Cohort Study. *Ann Intern Med*. 2020;172(7):463-73. Epub 20200310. doi: 10.7326/M19-2522. PubMed PMID: 32150751.
 99. Frost JL, Campos-Outcalt D, Hoelting D, LeFevre M, Lin KW, Vaughan W et al. Pharmacologic Management of Newly Detected Atrial Fibrillation. *American Academy of Family Physicians*; 2017 Apr. Available from: https://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/a-fib-guideline.pdf.
 100. Fukasawa T, Seki T, Nakashima M, Kawakami K. Comparative effectiveness and safety of edoxaban, rivaroxaban, and apixaban in patients with venous thromboembolism: A cohort study. *J Thromb Haemost*. 2022;20(9):2083-97. Epub 20220707. doi: 10.1111/jth.15799. PubMed PMID: 35748327.
 101. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes. *Adv Chronic Kidney Dis*. 2014;21(6):460-71. Epub 20141024. doi: 10.1053/j.ackd.2014.07.005. PubMed PMID: 25443571; PubMed Central PMCID: PMC4254470.
 102. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(12):e726-e79. Epub 20161113. doi: 10.1161/CIR.0000000000000471. PubMed PMID: 27840333; PubMed Central PMCID: PMC5477786.
 103. Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2013;128(24):2622-703. Epub 20131113. doi: 10.1161/01.cir.0000436140.77832.7a. PubMed PMID: 24226806.
 104. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2014;63(9):891-900. Epub 20131204. doi: 10.1016/j.jacc.2013.11.013. PubMed PMID: 24315894; PubMed Central PMCID: PMC4206565.
 105. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, et al. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *Am J Med*. 2019;132(5):596-604 e11. Epub 20190109. doi: 10.1016/j.amjmed.2018.12.023. PubMed PMID: 30639551.
 106. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with

- dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation*. 2015;131(2):157-64. Epub 20141030. doi: 10.1161/circulationaha.114.012061. PubMed PMID: 25359164.
107. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92. Epub 20110827. doi: 10.1056/NEJMoa1107039. PubMed PMID: 21870978.
108. Grymonprez M, De Backer TL, Bertels X, Steurbaut S, Lahousse L. Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: A nationwide cohort study. *Front Pharmacol*. 2023;14:1125576. Epub 20230202. doi: 10.3389/fphar.2023.1125576. PubMed PMID: 36817122; PubMed Central PMCID: PMC9932194.
109. Gupta K, Trocio J, Keshishian A, Zhang Q, Dina O, Mardekian J, et al. Real-World Comparative Effectiveness, Safety, and Health Care Costs of Oral Anticoagulants in Nonvalvular Atrial Fibrillation Patients in the U.S. Department of Defense Population. *J Manag Care Spec Pharm*. 2018;24(11):1116-27. Epub 20180913. doi: 10.18553/jmcp.2018.17488. PubMed PMID: 30212268; PubMed Central PMCID: PMC10398049.
110. Guzik TJ, Ramasundarahettige C, Pogossova N, Lopez-Jaramillo P, Dyal L, Berkowitz SD, et al. Rivaroxaban Plus Aspirin in Obese and Overweight Patients With Vascular Disease in the COMPASS Trial. *J Am Coll Cardiol*. 2021;77(5):511-25. doi: 10.1016/j.jacc.2020.11.061. PubMed PMID: 33538248.
111. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation*. 2014;130(2):138-46. Epub 20140603. doi: 10.1161/circulationaha.113.005008. PubMed PMID: 24895454.
112. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J*. 2014;35(28):1864-72. Epub 20140220. doi: 10.1093/eurheartj/ehu046. PubMed PMID: 24561548; PubMed Central PMCID: PMC4104493.
113. Han S, Han S, Suh HS, Bang OY, On YK, Lee MY, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation: A nationwide, population-based study in Korea. *J Arrhythm*. 2021;37(5):1240-9. Epub 20210811. doi: 10.1002/joa3.12607. PubMed PMID: 34621422; PubMed Central PMCID: PMC8485801.
114. Harrington J, Carnicelli AP, Hua K, Wallentin L, Patel MR, Hohnloser SH, et al. Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF. *Circulation*. 2023;147(23):1748-57. Epub 20230412. doi: 10.1161/circulationaha.122.062752. PubMed PMID: 37042255; PubMed Central PMCID: PMC10309661.
115. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12(8):464-74. Epub 20150616. doi: 10.1038/nrcardio.2015.83. PubMed PMID: 26076949; PubMed Central PMCID: PMC4624298.
116. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, et al. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to

- Renal Function Over Time: Insights From the ARISTOTLE Randomized Clinical Trial. *JAMA Cardiol.* 2016;1(4):451-60. doi: 10.1001/jamacardio.2016.1170. PubMed PMID: 27438322.
117. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612. PubMed PMID: 32860505.
 118. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism - a systematic review with indirect comparisons. *Vasa.* 2014;43(5):353-64. doi: 10.1024/0301-1526/a000373. PubMed PMID: 25147012.
 119. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J.* 2012;33(22):2821-30. Epub 20120829. doi: 10.1093/eurheartj/ehs274. PubMed PMID: 22933567.
 120. Houghton DE, Vlazny DT, Casanegra AI, Brunton N, Froehling DA, Meverden RA, et al. Bleeding in Patients With Gastrointestinal Cancer Compared With Nongastrointestinal Cancer Treated With Apixaban, Rivaroxaban, or Enoxaparin for Acute Venous Thromboembolism. *Mayo Clin Proc.* 2021;96(11):2793-805. Epub 20210820. doi: 10.1016/j.mayocp.2021.04.026. PubMed PMID: 34425962.
 121. Hsia J, Szarek M, Anand S, Patel MR, Debus S, Berkowitz SD, et al. Rivaroxaban in Patients With Recent Peripheral Artery Revascularization and Renal Impairment: The VOYAGER PAD Trial. *J Am Coll Cardiol.* 2021;78(7):757-9. doi: 10.1016/j.jacc.2021.06.021. PubMed PMID: 34384556.
 122. Impact of blood clots on the United States infographic [Internet]. Georgia: U.S. Centers for Disease Control and Prevention [cited 2023 Jul 1]. Available from: https://www.cdc.gov/blood-clots/toolkit/impact-of-blood-clots.html?CDC_AAref_Val=https://www.cdc.gov/ncbddd/dvt/infographic-impact.html.
 123. Ingason AB, Hreinsson JP, Agustsson AS, Lund SH, Rumba E, Palsson DA, et al. Comparison of the effectiveness and safety of direct oral anticoagulants: a nationwide propensity score-weighted study. *Blood Adv.* 2023;7(11):2564-72. doi: 10.1182/bloodadvances.2022009099. PubMed PMID: 36562754; PubMed Central PMCID: PMC10242633.
 124. Ingason AB, Hreinsson JP, Agustsson AS, Lund SH, Rumba E, Palsson DA, et al. Rivaroxaban Is Associated With Higher Rates of Gastrointestinal Bleeding Than Other Direct Oral Anticoagulants : A Nationwide Propensity Score-Weighted Study. *Ann Intern Med.* 2021;174(11):1493-502. Epub 20211012. doi: 10.7326/M21-1474. PubMed PMID: 34633836.
 125. Jaksa A, Gibbs L, Kent S, Rowark S, Duffield S, Sharma M, et al. Using primary care data to assess comparative effectiveness and safety of apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation in the UK: an observational cohort study. *BMJ Open.* 2022;12(10):e064662. Epub 20221017. doi: 10.1136/bmjopen-2022-064662. PubMed PMID: 36253039; PubMed Central PMCID: PMC9577930.
 126. Janssen Pharmaceuticals, Inc. Xarelto (rivaroxaban) [package insert]. U.S. Food and Drug Administration. 2023 Feb. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022406s041lbl.pdf.

127. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104. Epub 20140328. doi: 10.1161/CIR.0000000000000040. PubMed PMID: 24682348.
128. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e51. Epub 20190128. doi: 10.1161/CIR.0000000000000665. PubMed PMID: 30686041.
129. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *Bmj*. 2016;353:i2868. Epub 20160615. doi: 10.1136/bmj.i2868. PubMed PMID: 27306620; PubMed Central PMCID: PMC4908974.
130. Jin MC, Sussman ES, Feng AY, Han SS, Skirboll SL, Berube C, et al. Hemorrhage risk of direct oral anticoagulants in real-world venous thromboembolism patients. *Thromb Res*. 2021;204:126-33. Epub 20210627. doi: 10.1016/j.thromres.2021.06.015. PubMed PMID: 34198049.
131. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):e1-e156. Epub 20231130. doi: 10.1161/CIR.0000000000001193. PubMed PMID: 38033089; PubMed Central PMCID: PMC11095842.
132. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol*. 2015;116(2):230-5. Epub 20150416. doi: 10.1016/j.amjcard.2015.04.012. PubMed PMID: 26004053; PubMed Central PMCID: PMC4780330.
133. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S-e226S. doi: 10.1378/chest.11-2296. PubMed PMID: 22315261; PubMed Central PMCID: PMC3278052.
134. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020;38(5):496-520. Epub 20190805. doi: 10.1200/JCO.19.01461. PubMed PMID: 31381464.
135. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Guideline Update. *J Clin Oncol*. 2023;41(16):3063-71. Epub 20230419. doi: 10.1200/JCO.23.00294. PubMed PMID: 37075273.
136. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic

- Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467. Epub 20210524. doi: 10.1161/STR.0000000000000375. PubMed PMID: 34024117.
137. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Korv J, Lal A, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J*. 2019;4(3):198-223. Epub 20190409. doi: 10.1177/2396987319841187. PubMed PMID: 31984228; PubMed Central PMCID: PMC6960695.
 138. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603. doi: 10.1093/eurheartj/ehz405. PubMed PMID: 31504429.
 139. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res*. 2020;127(1):4-20. Epub 20200618. doi: 10.1161/circresaha.120.316340. PubMed PMID: 32716709; PubMed Central PMCID: PMC7577553.
 140. Krantz MJ, Debus SE, Hsia J, Patel MR, Anand SS, Nehler MR, et al. Low-dose rivaroxaban plus aspirin in older patients with peripheral artery disease undergoing acute limb revascularization: insights from the VOYAGER PAD trial. *Eur Heart J*. 2021;42(39):4040-8. doi: 10.1093/eurheartj/ehab408. PubMed PMID: 34430972.
 141. LaMori JC, Mody SH, Gross HJ, daCosta DiBonaventura M, Patel AA, Schein JR, et al. Burden of comorbidities among patients with atrial fibrillation. *Ther Adv Cardiovasc Dis*. 2013;7(2):53-62. Epub 20121022. doi: 10.1177/1753944712464101. PubMed PMID: 23090783.
 142. Lau WCY, Torre CO, Man KKC, Stewart HM, Seager S, Van Zandt M, et al. Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation: A Multinational Population-Based Cohort Study. *Ann Intern Med*. 2022;175(11):1515-24. Epub 20221101. doi: 10.7326/M22-0511. PubMed PMID: 36315950.
 143. Lawal OD, Aronow HD, Shobayo F, Hume AL, Taveira TH, Matson KL, et al. Comparative Effectiveness and Safety of Direct Oral Anticoagulants and Warfarin in Patients With Atrial Fibrillation and Chronic Liver Disease: A Nationwide Cohort Study. *Circulation*. 2023;147(10):782-94. Epub 20230210. doi: 10.1161/CIRCULATIONAHA.122.060687. PubMed PMID: 36762560.
 144. Lee SR, Choi EK, Kwon S, Han KD, Jung JH, Cha MJ, et al. Effectiveness and Safety of Contemporary Oral Anticoagulants Among Asians With Nonvalvular Atrial Fibrillation. *Stroke*. 2019;50(8):2245-9. Epub 20190618. doi: 10.1161/STROKEAHA.119.025536. PubMed PMID: 31208303.
 145. Lewis S, Glen J, Dawoud D, Dias S, Cobb J, Griffin X, et al. Venous Thromboembolism Prophylaxis Strategies for People Undergoing Elective Total Hip Replacement: A Systematic Review and Network Meta-Analysis. *Value Health*. 2019;22(8):953-69. Epub 20190517. doi: 10.1016/j.jval.2019.02.013. PubMed PMID: 31426937.
 146. Li D, Liu Y, Song Y, Wen A. Antithrombotic therapy for secondary prevention of unprovoked venous thromboembolism: a systematic review and network meta-analysis of randomized

- controlled trials. *Ann Med*. 2022;54(1):253-61. doi: 10.1080/07853890.2022.2026002. PubMed PMID: 35023788; PubMed Central PMCID: PMC8759723.
147. Li G, Lip GYH, Holbrook A, Chang Y, Larsen TB, Sun X, et al. Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. *Eur J Epidemiol*. 2019;34(2):173-90. Epub 20180608. doi: 10.1007/s10654-018-0415-7. PubMed PMID: 29948370.
148. Li G, Zeng J, Zhang J, Thabane L. Comparative Effects Between Direct Oral Anticoagulants for Acute Venous Thromboembolism: Indirect Comparison From Randomized Controlled Trials. *Front Med (Lausanne)*. 2020;7:280. Epub 20200619. doi: 10.3389/fmed.2020.00280. PubMed PMID: 32637418; PubMed Central PMCID: PMC7316891.
149. Lin J, Trocio J, Gupta K, Mardekian J, Lingohr-Smith M, Menges B, et al. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. *J Med Econ*. 2017;20(9):952-61. Epub 20170622. doi: 10.1080/13696998.2017.1341902. PubMed PMID: 28604139.
150. Lin S, Wang Y, Zhang L, Guan W. Dabigatran must be used carefully: literature review and recommendations for management of adverse events. *Drug Des Devel Ther*. 2019;13:1527-33. Epub 20190506. doi: 10.2147/DDDT.S203112. PubMed PMID: 31190734; PubMed Central PMCID: PMC6511609.
151. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost*. 2016;116(5):975-86. Epub 20160819. doi: 10.1160/TH16-05-0403. PubMed PMID: 27538358.
152. Lip GY, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, et al. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. *Int J Clin Pract*. 2016;70(9):752-63. Epub 20160823. doi: 10.1111/ijcp.12863. PubMed PMID: 27550177; PubMed Central PMCID: PMC5129572.
153. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;154(5):1121-201. Epub 20180822. doi: 10.1016/j.chest.2018.07.040. PubMed PMID: 30144419.
154. Lip GYH, Keshishian A, Kang A, Dhamane AD, Luo X, Klem C, et al. Effectiveness and safety of oral anticoagulants among non-valvular atrial fibrillation patients with polypharmacy. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(5):405-14. doi: 10.1093/ehjcvp/pvaa117. PubMed PMID: 33010157.
155. Lip GYH, Keshishian A, Kang A, Luo X, Atreja N, Zhang Y, et al. Effectiveness and safety of oral anticoagulants in non-valvular atrial fibrillation patients with prior bleeding events: a retrospective analysis of administrative claims databases. *J Thromb Thrombolysis*. 2022;54(1):33-46. Epub 20220517. doi: 10.1007/s11239-022-02660-2. PubMed PMID: 35579733; PubMed Central PMCID: PMC9259524.
156. Lip GYH, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. *Stroke*. 2018;49(12):2933-44. doi: 10.1161/STROKEAHA.118.020232. PubMed PMID: 30571400; PubMed Central PMCID: PMC6257512.

157. Lip GYH, Keshishian AV, Kang AL, Dhamane AD, Luo X, Li X, et al. Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study. *J Intern Med*. 2021;289(1):42-52. Epub 20200716. doi: 10.1111/joim.13140. PubMed PMID: 32602228.
158. Lip GYH, Keshishian AV, Kang AL, Li X, Dhamane AD, Luo X, et al. Effectiveness and Safety of Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Diabetes Mellitus. *Mayo Clin Proc*. 2020;95(5):929-43. doi: 10.1016/j.mayocp.2019.05.032. PubMed PMID: 32370854.
159. Lip GYH, Keshishian AV, Zhang Y, Kang A, Dhamane AD, Luo X, et al. Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With High Risk of Gastrointestinal Bleeding. *JAMA Netw Open*. 2021;4(8):e2120064. Epub 20210802. doi: 10.1001/jamanetworkopen.2021.20064. PubMed PMID: 34398204; PubMed Central PMCID: PMC8369361.
160. Lip GYH, Kotalczyk A, Teutsch C, Diener HC, Dubner SJ, Halperin JL, et al. Comparative effectiveness and safety of non-vitamin K antagonists for atrial fibrillation in clinical practice: GLORIA-AF Registry. *Clin Res Cardiol*. 2022;111(5):560-73. Epub 20220316. doi: 10.1007/s00392-022-01996-2. PubMed PMID: 35294625; PubMed Central PMCID: PMC9054878.
161. Lopes RD, Thomas L, Di Fusco M, Keshishian A, Luo X, Li X, et al. Clinical and Economic Outcomes Among Nonvalvular Atrial Fibrillation Patients With Coronary Artery Disease and/or Peripheral Artery Disease. *Am J Cardiol*. 2021;148:69-77. Epub 20210303. doi: 10.1016/j.amjcard.2021.02.021. PubMed PMID: 33667438.
162. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ*. 2017;359:j5058. Epub 20171128. doi: 10.1136/bmj.j5058. PubMed PMID: 29183961; PubMed Central PMCID: PMC5704695.
163. Lutsey PL, Zakai NA, MacLehose RF, Norby FL, Walker RF, Roetker NS, et al. Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism. *Br J Haematol*. 2019;185(5):903-11. Epub 20190328. doi: 10.1111/bjh.15857. PubMed PMID: 30919942; PubMed Central PMCID: PMC6536346.
164. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5(4):927-74. doi: 10.1182/bloodadvances.2020003442. PubMed PMID: 33570602; PubMed Central PMCID: PMC7903232.
165. Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol*. 2020;7(1):e18-e27. Epub 20191105. doi: 10.1016/s2352-3026(19)30219-4. PubMed PMID: 31699660.
166. Mando R, Waheed M, Michel A, Karabon P, Halalau A. Prediabetes as a risk factor for major adverse cardiovascular events. *Ann Med*. 2021;53(1):2090-8. doi: 10.1080/07853890.2021.2000633. PubMed PMID: 34761971; PubMed Central PMCID: PMC8592612.
167. Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med*. 2012;28(2):287-300. doi: 10.1016/j.cger.2012.01.008. PubMed PMID: 22500544; PubMed Central PMCID: PMC3335752.

168. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost.* 2021;19(8):1874-82. Epub 20210714. doi: 10.1111/jth.15358. PubMed PMID: 34259389.
169. Mazzolai L, Ageno W, Alatri A, Bauersachs R, Becattini C, Brodmann M, et al. Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. *Eur J Prev Cardiol.* 2022;29(8):1248-63. doi: 10.1093/eurjpc/zwab088. PubMed PMID: 34254133.
170. McCrindle BW, Michelson AD, Van Bergen AH, Horowitz ES, Sandoval JP, Justino H, et al. Thromboprophylaxis for Children Post-Fontan Procedure: Insights From the UNIVERSE Study. *J Am Heart Assoc.* 2021;10(22):e021765. Epub 20210924. doi: 10.1161/jaha.120.021765. PubMed PMID: 34558312; PubMed Central PMCID: PMC8751951.
171. McHorney CA, Ashton V, Laliberté F, Germain G, Wynant W, Crivera C, et al. Adherence to Rivaroxaban Compared with Other Oral Anticoagulant Agents Among Patients with Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm.* 2017;23(9):980-8. doi: 10.18553/jmcp.2017.23.9.980. PubMed PMID: 28854075; PubMed Central PMCID: PMC10397742.
172. McHorney CA, Crivera C, Laliberté F, Germain G, Wynant W, Lefebvre P. Adherence to rivaroxaban versus apixaban among patients with non-valvular atrial fibrillation: Analysis of overall population and subgroups of prior oral anticoagulant users. *PLoS One.* 2018;13(4):e0194099. Epub 20180405. doi: 10.1371/journal.pone.0194099. PubMed PMID: 29621248; PubMed Central PMCID: PMC5886396.
173. McHorney CA, Crivera C, Laliberté F, Nelson WW, Germain G, Bookhart B, et al. Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure. *Curr Med Res Opin.* 2015;31(12):2167-73. Epub 20151022. doi: 10.1185/03007995.2015.1096242. PubMed PMID: 26393483.
174. McHorney CA, Peterson ED, Ashton V, Laliberté F, Crivera C, Germain G, et al. Modeling the impact of real-world adherence to once-daily (QD) versus twice-daily (BID) non-vitamin K antagonist oral anticoagulants on stroke and major bleeding events among non-valvular atrial fibrillation patients. *Curr Med Res Opin.* 2019;35(4):653-60. Epub 20181030. doi: 10.1080/03007995.2018.1530205. PubMed PMID: 30265159.
175. McHorney CA, Peterson ED, Laliberté F, Germain G, Nelson WW, Crivera C, et al. Comparison of Adherence to Rivaroxaban Versus Apixaban Among Patients With Atrial Fibrillation. *Clin Ther.* 2016;38(11):2477-88. Epub 20161024. doi: 10.1016/j.clinthera.2016.09.014. PubMed PMID: 27789043.
176. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, et al. Efficacy and Safety of Apixaban Versus Warfarin in Patients with Atrial Fibrillation and a History of Cancer: Insights from the ARISTOTLE Trial. *Am J Med.* 2017;130(12):1440-8.e1. Epub 20170721. doi: 10.1016/j.amjmed.2017.06.026. PubMed PMID: 28739198.
177. Memon RA, Hamdani SSQ, Usama A, Aisha F, Kundi H, Mathavan M, et al. Comparison of the Efficacy and Safety of Apixaban and Warfarin in the Prevention of Stroke in Patients With Non-valvular Atrial Fibrillation: A Meta-Analysis. *Cureus.* 2022;14(8):e27838. Epub

20220809. doi: 10.7759/cureus.27838. PubMed PMID: 36134060; PubMed Central PMCID: PMC9481239.
178. Mentias A, Heller E, Vaughan Sarrazin M. Comparative Effectiveness of Rivaroxaban, Apixaban, and Warfarin in Atrial Fibrillation Patients With Polypharmacy. *Stroke*. 2020;51(7):2076-86. Epub 20200610. doi: 10.1161/STROKEAHA.120.029541. PubMed PMID: 32517580; PubMed Central PMCID: PMC7388787.
 179. Merli GJ, Hollander JE, Lefebvre P, Laliberte F, Raut MK, Germain G, et al. Costs of hospital visits among patients with deep vein thrombosis treated with rivaroxaban and LMWH/warfarin. *J Med Econ*. 2016;19(1):84-90. Epub 20151027. doi: 10.3111/13696998.2015.1096274. PubMed PMID: 26390315.
 180. Miao B, Sood N, Bunz TJ, Coleman CI. Rivaroxaban versus apixaban in non-valvular atrial fibrillation patients with end-stage renal disease or receiving dialysis. *Eur J Haematol*. 2020;104(4):328-35. Epub 20200129. doi: 10.1111/ejh.13383. PubMed PMID: 31925840.
 181. Milentijevic D, Germain G, Laliberté F, Bookhart BK, MacKnight SD, Tsang J, et al. Healthcare costs of NVAf patients treated with rivaroxaban and apixaban in the US. *J Med Econ*. 2020;23(11):1365-74. Epub 20200929. doi: 10.1080/13696998.2020.1821038. PubMed PMID: 32897766.
 182. Minges KE, Bikdeli B, Wang Y, Attaran RR, Krumholz HM. National and Regional Trends in Deep Vein Thrombosis Hospitalization Rates, Discharge Disposition, and Outcomes for Medicare Beneficiaries. *Am J Med*. 2018;131(10):1200-8. Epub 20180623. doi: 10.1016/j.amjmed.2018.04.033. PubMed PMID: 29753792; PubMed Central PMCID: PMC7040884.
 183. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e737S-e801S. doi: 10.1378/chest.11-2308. PubMed PMID: 22315277; PubMed Central PMCID: PMC3278066.
 184. Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292-316. doi: 10.1182/bloodadvances.2018024786. PubMed PMID: 30482766; PubMed Central PMCID: PMC6258911.
 185. Nasiri A, AlQahtani A, Rayes NH, AlQahtani R, Alkharras R, Alghethber H. Direct oral anticoagulant: Review article. *J Family Med Prim Care*. 2022;11(8):4180-3. Epub 20220830. doi: 10.4103/jfmpc.jfmpc_2253_21. PubMed PMID: 36352947; PubMed Central PMCID: PMC9638657.
 186. National Center on Birth Defects and Developmental Disabilities. Impact of Blood Clots on the United States. U.S. Centers for Disease Control and Prevention; 2023 Jun 28. Available from: <https://web.archive.org/web/20240515064620/https://www.cdc.gov/ncbddd/dvt/infographic-impact.html#:~:text=VTE%20affects%20as%20many%20as%20900%2C000%20Americans%20each,clot%20will%20have%20another%20episode%20within%2010%20years.>

187. National Guideline Centre (UK). Venous thromboembolism in over 16s: Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. London: National Institute for Health and Care Excellence (NICE); 2018 Mar. PubMed PMID: 29697228.
188. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60(3):686-95 e2. Epub 20140510. doi: 10.1016/j.jvs.2014.03.290. PubMed PMID: 24820900.
189. Neumann I, Izcovich A, Zhang Y, Rada G, Kahn SR, Spencer F, et al. DOACs vs LMWHs in hospitalized medical patients: a systematic review and meta-analysis that informed 2018 ASH guidelines. *Blood Adv*. 2020;4(7):1512-7. doi: 10.1182/bloodadvances.2019000840. PubMed PMID: 32289163; PubMed Central PMCID: PMC7160267.
190. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-7. doi: 10.1056/NEJMp1405158. PubMed PMID: 25162885.
191. Nguyen E, Weeda ER, Sobieraj DM, Bookhart BK, Piech CT, Coleman CI. Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review. *Curr Med Res Opin*. 2016;32(7):1281-90. Epub 20160401. doi: 10.1185/03007995.2016.1170673. PubMed PMID: 27033747.
192. Nicolaidis AN, Fareed J, Spyropoulos AC, Kakkar RHL, Antignani PL, Avgerinos E, et al. Prevention and management of venous thromboembolism. International Consensus Statement. Guidelines according to scientific evidence. *Int Angiol*. 2024;43(1):1-222. doi: 10.23736/S0392-9590.23.05177-5. PubMed PMID: 38421381.
193. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation. *Chest*. 2016;150(6):1302-12. Epub 20160928. doi: 10.1016/j.chest.2016.07.013. PubMed PMID: 27938741.
194. Office of Minority Health. Diabetes disparities in Medicare fee-for-service beneficiaries. Centers for Medicare and Medicaid Services; 2024 Apr. Available from: <https://www.cms.gov/About-CMS/Agency-Information/OMH/Downloads/Data-Snapshots-Diabetes.pdf>.
195. Office of Minority Health. Obesity disparities in Medicare fee-for-service beneficiaries. Centers for Medicare and Medicaid Services; 2022 Jan. Available from: <https://www.cms.gov/files/document/omh-datasnapshot-obesity.pdf>.
196. Office of Minority Health. Stroke disparities in Medicare fee-for-service beneficiaries. Centers for Medicare and Medicaid Services; 2021 Jul. Available from: <https://www.cms.gov/files/document/omhdatasnapshot-strokepdf.pdf>.
197. Okushi Y, Kusunose K, Nakai M, Sumita Y, Ise T, Yamaguchi K, et al. Comparison of Direct Oral Anticoagulants for Acute Hospital Mortality in Venous Thromboembolism. *Am J Cardiovasc Drugs*. 2022;22(4):407-16. Epub 20211220. doi: 10.1007/s40256-021-00514-5. PubMed PMID: 34927214.
198. Olesen KKW, Gyldenkerne C, Thim T, Thomsen RW, Maeng M. Peripheral artery disease, lower limb revascularization, and amputation in diabetes patients with and without coronary artery disease: a cohort study from the Western Denmark Heart Registry. *BMJ Open Diabetes Res Care*. 2021;9(1). doi: 10.1136/bmjdr-2020-001803. PubMed PMID: 33414173; PubMed Central PMCID: PMC7797253.

199. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4(19):4693-738. doi: 10.1182/bloodadvances.2020001830. PubMed PMID: 33007077; PubMed Central PMCID: PMC7556153.
200. PAD National Action Plan. American Heart Association; 2022 May. Available from: <https://professional.heart.org/-/media/PHD-Files-2/Science-News/p/PAD-National-Action-Plan.pdf>.
201. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-91. Epub 20110810. doi: 10.1056/NEJMoa1009638. PubMed PMID: 21830957.
202. Pawar A, Gagne JJ, Gopalakrishnan C, Iyer G, Tesfaye H, Brill G, et al. Association of Type of Oral Anticoagulant Dispensed With Adverse Clinical Outcomes in Patients Extending Anticoagulation Therapy Beyond 90 Days After Hospitalization for Venous Thromboembolism. *JAMA.* 2022;327(11):1051-60. doi: 10.1001/jama.2022.1920. PubMed PMID: 35289881; PubMed Central PMCID: PMC8924711.
203. Perreault S, Dragomir A, Cote R, Lenglet A, de Denus S, Dorais M, et al. Comparative Effectiveness and Safety of Low-Dose Oral Anticoagulants in Patients With Atrial Fibrillation. *Front Pharmacol.* 2021;12:812018. Epub 20220114. doi: 10.3389/fphar.2021.812018. PubMed PMID: 35095525; PubMed Central PMCID: PMC8795908.
204. Perreault S, Dragomir A, Cote R, Lenglet A, White-Guay B, de Denus S, et al. Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: A propensity score-matched cohort study. *Pharmacotherapy.* 2021;41(4):379-93. Epub 20210227. doi: 10.1002/phar.2509. PubMed PMID: 33544915.
205. Phillips AR, Reitz KM, Myers S, Thoma F, Andraska EA, Jano A, et al. Association Between Black Race, Clinical Severity, and Management of Acute Pulmonary Embolism: A Retrospective Cohort Study. *J Am Heart Assoc.* 2021;10(17):e021818. Epub 20210825. doi: 10.1161/jaha.121.021818. PubMed PMID: 34431356; PubMed Central PMCID: PMC8649302.
206. Piccini JP, Garg J, Patel MR, Likhnygina Y, Goodman SG, Becker RC, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. *Eur Heart J.* 2014;35(28):1873-80. Epub 20140321. doi: 10.1093/eurheartj/ehu083. PubMed PMID: 24658769.
207. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, Berkowitz SD, et al. Polypharmacy and the Efficacy and Safety of Rivaroxaban Versus Warfarin in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation. *Circulation.* 2016;133(4):352-60. Epub 20151216. doi: 10.1161/circulationaha.115.018544. PubMed PMID: 26673560.
208. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. *Circulation.* 2022;146(23):1735-45. Epub 20221106. doi: 10.1161/circulationaha.121.054990. PubMed PMID: 36335914.
209. Polzin A, Helten C, Metzen D, Zako S, Veulemans V, Kelm M, Zeus T. TAVR: nemesis of NOACs? *J Thromb Thrombolysis.* 2023;55(1):181-4. Epub 20221101. doi: 10.1007/s11239-022-02721-6. PubMed PMID: 36318378; PubMed Central PMCID: PMC9925602.

210. Prevalence state/county level all beneficiaries by age [Internet]. Maryland: Centers for Medicare and Medicaid Services. 2007-2018 [cited 2023 Jul 27]. Available from: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/downloads/cc_prev_state_county_age.zip.
211. Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21. Epub 20130920. doi: 10.1186/1477-9560-11-21. PubMed PMID: 24053656; PubMed Central PMCID: PMC3850944.
212. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 9875401, Rivaroxaban; [cited 2023 Aug 24]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Rivaroxaban>.
213. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 10182969, Apixaban; [cited 2023 Aug 24]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Apixaban>.
214. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 10280735, Edoxaban; [cited 2023 Aug 24]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Edoxaban>.
215. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 216210, Dabigatran; [cited 2023 Aug 24]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Dabigatran>.
216. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 54678486, Warfarin; [cited 2023 Aug 24]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Warfarin>.
217. PubChem [Internet]. Maryland: National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 16667706, ENOXAPARIN SODIUM (1% wt/vol in 10%aq DMSO); [cited 2023 Aug 24]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/ENOXAPARIN-SODIUM-_1_-wt_vol-in-10_aq-DMSO.
218. Ramacciotti E, Weitz JI. Rivaroxaban plus aspirin for cardiovascular protection: Rationale for the vascular dose and dual pathway inhibition. *Thrombosis Research*. 2019;184:44-9. doi: 10.1016/j.thromres.2019.09.033.
219. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. *JAMA*. 2018;320(21):2221-30. doi: 10.1001/jama.2018.17242. PubMed PMID: 30512099; PubMed Central PMCID: PMC6404233.
220. Ray WA, Chung CP, Stein CM, Smalley W, Zimmerman E, Dupont WD, et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial

- Fibrillation. *JAMA*. 2021;326(23):2395-404. doi: 10.1001/jama.2021.21222. PubMed PMID: 34932078; PubMed Central PMCID: PMC8693217.
221. Rivera-Caravaca JM, Camelo-Castillo A, Ramirez-Macias I, Gil-Perez P, Lopez-Garcia C, Esteve-Pastor MA, et al. Antithrombotic Therapy in Patients with Peripheral Artery Disease: A Focused Review on Oral Anticoagulation. *Int J Mol Sci*. 2021;22(13). Epub 20210701. doi: 10.3390/ijms22137113. PubMed PMID: 34281167; PubMed Central PMCID: PMC8267774.
 222. Rutherford OW, Jonasson C, Ghanima W, Soderdahl F, Halvorsen S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2020;6(2):75-85. doi: 10.1093/ehjcvp/pvz086. PubMed PMID: 31942972; PubMed Central PMCID: PMC7073510.
 223. Rutherford OW, Jonasson C, Ghanima W, Soderdahl F, Halvorsen S. Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. *Heart*. 2022;108(5):345-52. Epub 20210511. doi: 10.1136/heartjnl-2020-318753. PubMed PMID: 33975877; PubMed Central PMCID: PMC8862105.
 224. Salerno DM, Thornberg ME, Lange NW, Hedvat J, Robbins H, Brown RS, et al. Less bleeding associated with apixaban versus other direct acting oral anticoagulation in solid organ transplant recipients. *Clin Transplant*. 2021;35(12):e14396. Epub 20211206. doi: 10.1111/ctr.14396. PubMed PMID: 34165845.
 225. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. 2016;316(10):1093-103. doi: 10.1001/jama.2016.12195. PubMed PMID: 27623463.
 226. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74(14):1823-38. doi: 10.1016/j.jacc.2019.08.1017. PubMed PMID: 31582143.
 227. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154-62. Epub 20150507. doi: 10.1016/s0140-6736(14)61774-8. PubMed PMID: 25960110; PubMed Central PMCID: PMC4553037.
 228. Schunemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198-225. doi: 10.1182/bloodadvances.2018022954. PubMed PMID: 30482763; PubMed Central PMCID: PMC6258910.
 229. Shermock KM, Lau BD, Haut ER, Hobson DB, Ganetsky VS, Kraus PS, et al. Patterns of non-administration of ordered doses of venous thromboembolism prophylaxis: implications for novel intervention strategies. *PLoS One*. 2013;8(6):e66311. Epub 20130614. doi: 10.1371/journal.pone.0066311. PubMed PMID: 23799091; PubMed Central PMCID: PMC3683023.
 230. Spyropoulos AC, Lipardi C, Xu J, Lu W, Suh E, Yuan Z, et al. Improved Benefit Risk Profile of Rivaroxaban in a Subpopulation of the MAGELLAN Study. *Clin Appl Thromb Hemost*. 2019;25:1076029619886022. doi: 10.1177/1076029619886022. PubMed PMID: 31746218; PubMed Central PMCID: PMC7019408.
 231. Stanifer JW, Pokorney SD, Chertow GM, Hohnloser SH, Wojdyla DM, Garonzik S, et al. Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney

- Disease. *Circulation*. 2020;141(17):1384-92. Epub 20200312. doi: 10.1161/circulationaha.119.044059. PubMed PMID: 32160801.
232. Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS Trial: Net Clinical Benefit of Low-Dose Rivaroxaban Plus Aspirin as Compared With Aspirin in Patients With Chronic Vascular Disease. *Circulation*. 2020;142(1):40-8. Epub 20200521. doi: 10.1161/circulationaha.120.046048. PubMed PMID: 32436455.
233. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021;160(6):e545-e608. Epub 20210802. doi: 10.1016/j.chest.2021.07.055. PubMed PMID: 34352278.
234. Strilciuc S, Grad DA, Radu C, Chira D, Stan A, Ungureanu M, et al. The economic burden of stroke: a systematic review of cost of illness studies. *J Med Life*. 2021;14(5):606-19. doi: 10.25122/jml-2021-0361. PubMed PMID: 35027963; PubMed Central PMCID: PMC8742896.
235. Talmor-Barkan Y, Yacovzada NS, Rossman H, Witberg G, Kalka I, Kornowski R, et al. Head-to-head efficacy and safety of rivaroxaban, apixaban, and dabigatran in an observational nationwide targeted trial. *Eur Heart J Cardiovasc Pharmacother*. 2022;9(1):26-37. doi: 10.1093/ehjcvp/pvac063. PubMed PMID: 36341531.
236. Tepper PG, Mardekian J, Masseria C, Phatak H, Kamble S, Abdulsattar Y, et al. Real-world comparison of bleeding risks among non-valvular atrial fibrillation patients prescribed apixaban, dabigatran, or rivaroxaban. *PLoS One*. 2018;13(11):e0205989. Epub 20181101. doi: 10.1371/journal.pone.0205989. PubMed PMID: 30383768; PubMed Central PMCID: PMC6211674.
237. The American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria(R) for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(7):2052-81. Epub 20230504. doi: 10.1111/jgs.18372. PubMed PMID: 37139824.
238. Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World J Diabetes*. 2015;6(7):961-9. doi: 10.4239/wjd.v6.i7.961. PubMed PMID: 26185603; PubMed Central PMCID: PMC4499529.
239. Tice J, Richardson M, Wright A, Seidner M, Rind D, Pearson S. Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto. Institute for Clinical and Economic Review 2023 Oct 2. Available from: https://icer.org/wp-content/uploads/2023/09/ICER_NVAF_Medicare_Assessment_100223.pdf.
240. Tice JA, Richardson M, Wright A, Seidner M, Rind DM, Pearson SD. Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto - Supplemental Materials. Institute for Clinical and Economic Review; 2023 Oct 2. Available from: https://icer.org/wp-content/uploads/2023/09/ICER_NVAF_Medicare_Supplement_100223.pdf
241. Tritschler T, Aujesky D. Venous thromboembolism in the elderly: A narrative review. *Thromb Res*. 2017;155:140-7. Epub 20170517. doi: 10.1016/j.thromres.2017.05.015. PubMed PMID: 28550759.
242. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*. 2023;147(8):e93-e621. Epub 20230125. doi: 10.1161/CIR.0000000000001123. PubMed PMID: 36695182.

243. Underlying Cause of Death, 1999-2020 [Internet]. Centers for Disease Control and Prevention [cited 2023 Sep 11]. Available from: <https://wonder.cdc.gov/Deaths-by-Underlying-Cause.html>.
244. Van den Eynde J, Possner M, Alahdab F, Veldtman G, Goldstein BH, Rathod RH, et al. Thromboprophylaxis in Patients With Fontan Circulation. *J Am Coll Cardiol*. 2023;81(4):374-89. doi: 10.1016/j.jacc.2022.10.037. PubMed PMID: 36697138; PubMed Central PMCID: PMC11040452.
245. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;362:k2505. Epub 20180704. doi: 10.1136/bmj.k2505. PubMed PMID: 29973392; PubMed Central PMCID: PMC6031213.
246. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143(8):e254-e743. Epub 20210127. doi: 10.1161/CIR.0000000000000950. PubMed PMID: 33501848.
247. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148(9):e9-e119. Epub 20230720. doi: 10.1161/CIR.0000000000001168. PubMed PMID: 37471501.
248. Weeda ER, Nguyen E, Martin S, Ingham M, Sobieraj DM, Bookhart BK, et al. The impact of non-medical switching among ambulatory patients: an updated systematic literature review. *J Mark Access Health Policy*. 2019;7(1):1678563. Epub 20191019. doi: 10.1080/20016689.2019.1678563. PubMed PMID: 31692904; PubMed Central PMCID: PMC6818107.
249. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med*. 2017;376(13):1211-22. Epub 20170318. doi: 10.1056/NEJMoa1700518. PubMed PMID: 28316279.
250. Wells GA, Kelly S, Elliott J, Carrier M, Hsieh S, Chen L, et al. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: A Systematic Review and Network Meta-Analysis. University of Ottawa Heart Institute; 2016 Jan. Available from: <https://www.ottawaheart.ca/sites/default/files/legacy/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf>.
251. Willems LH, Maas D, Kramers K, Reijnen M, Riksen NP, Ten Cate H, et al. Antithrombotic Therapy for Symptomatic Peripheral Arterial Disease: A Systematic Review and Network Meta-Analysis. *Drugs*. 2022;82(12):1287-302. Epub 20220823. doi: 10.1007/s40265-022-01756-6. PubMed PMID: 35997941; PubMed Central PMCID: PMC9499921.
252. Wong A, Kraus PS, Lau BD, Streiff MB, Haut ER, Hobson DB, et al. Patient preferences regarding pharmacologic venous thromboembolism prophylaxis. *J Hosp Med*. 2015;10(2):108-11. Epub 20141122. doi: 10.1002/jhm.2282. PubMed PMID: 25418208.
253. Writing Committee Members, Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VES Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice

- Guidelines. *J Am Coll Cardiol*. 2024;83(24):2497-604. Epub 20240514. doi: 10.1016/j.jacc.2024.02.013. PubMed PMID: 38752899.
254. Wysokinski WE, Houghton DE, Casanegra AI, Vlazny DT, Bott-Kitslaar DM, Froehling DA, et al. Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism. *Am J Hematol*. 2019;94(11):1185-92. Epub 20190819. doi: 10.1002/ajh.25604. PubMed PMID: 31378995.
255. Xcenda. Issue Brief: Assessing the impact of formulary exclusion on healthcare costs and outcomes for patients on therapy for certain chronic conditions. AmerisourceBergen; 2023 May. Available from: <https://www.xcenda.com/insights/assessing-impact-formulary-exclusion-costs-outcomes-chronic-conditions>.
256. Yang L, Brooks MM, Glynn NW, Zhang Y, Saba S, Hernandez I. Real-World Direct Comparison of the Effectiveness and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Medicare Beneficiaries With Atrial Fibrillation. *Am J Cardiol*. 2020;126:29-36. Epub 20200410. doi: 10.1016/j.amjcard.2020.03.034. PubMed PMID: 32359718; PubMed Central PMCID: PMC7275920.
257. Yao X, Inselman JW, Ross JS, Izem R, Graham DJ, Martin DB, et al. Comparative Effectiveness and Safety of Oral Anticoagulants Across Kidney Function in Patients With Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes*. 2020;13(10):e006515. Epub 20201005. doi: 10.1161/CIRCOUTCOMES.120.006515. PubMed PMID: 33012172; PubMed Central PMCID: PMC7580213.
258. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol*. 2017;69(23):2779-90. doi: 10.1016/j.jacc.2017.03.600. PubMed PMID: 28595692.
259. Zhang J, Wang X, Liu X, Larsen TB, Witt DM, Ye Z, et al. Comparative effectiveness and safety of direct acting oral anticoagulants in nonvalvular atrial fibrillation for stroke prevention: a systematic review and meta-analysis. *Eur J Epidemiol*. 2021;36(8):793-812. Epub 20210515. doi: 10.1007/s10654-021-00751-7. PubMed PMID: 33993379.
260. Zhou B, Seabury S, Goldman D, Joyce G. Formulary restrictions and stroke risk in patients with atrial fibrillation. *Am J Manag Care*. 2022;28(10):521-8. doi: 10.37765/ajmc.2022.89195. PubMed PMID: 36252171.

Redacted Negotiation Meeting Summaries for Xarelto

Below are summaries of the negotiation meetings between CMS and the Primary Manufacturer, which include redacted information regarding the negotiation meetings and exchange of offers and counteroffers in the meetings.



SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Janssen Pharms regarding Xarelto on May 1, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Janssen Pharms (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Xarelto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, CMS invited the Primary Manufacturer to a negotiation meeting when rejecting the Primary Manufacturer’s counteroffer, and the Primary Manufacturer accepted CMS’ invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the first negotiation meeting, which was held on May 1, 2024 between 9:30 AM ET and 12:00 PM ET.

CMS Attendees:

1. Kaitlin Hunter, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
5. Lee Staley, Representative from the Office of the General Counsel
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

1. Lee Blevins, Senior Director, Strategic Account Managers for Emerging Government Policy
2. Ante Harxhi, MD, MBA, Senior Director, Therapeutic Area and Medical Innovation Lead
3. Perry Knight, JD, MHA, Vice President, Law
4. Shanthy Krishnarajah, MPH, MBA/MS, PhD, Senior Director, Scientific Evidence and Policy Research - New Products and IRA
5. Jacqueline Roche, DrPH, Head, Payment and Delivery Reform, Government Affairs and Policy
6. John Schaeffer, MBA, Senior Director, Strategy and Operations for Emerging Government Policy

Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- CMS to walk through their procedural approach for developing an initial offer, including:
 - Process for evaluating the clinical value for each indication
 - Understanding of how CMS translated clinical rating Likert scales to initial price offer
 - Understanding of CMS methodology for incorporating 'additional factors' in establishing clinical benefit and an upward/downward adjustment

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

- Review of Janssen's appropriate therapeutic alternatives for this exercise and other elements in rebuttal to CMS proposed Initial Price Offer
- CMS assessment of Janssen's counteroffer based on initial offer and procedural approach
- Next steps

Offers/Counteroffers Exchanged:





SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Janssen Pharms regarding Xarelto on June 3, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Janssen Pharms (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Xarelto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the first negotiation meeting held on May 1, 2024, each party had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. CMS requested a second negotiation meeting and the Primary Manufacturer accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the second negotiation meeting, which was held on June 3, 2024 between 1:30 PM ET and 4:00 PM ET.

CMS Attendees:

1. Kaitlin Hunter, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
5. Lee Staley, Representative from the Office of the General Counsel
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

1. Lee Blevins, Senior Director, Strategic Account Managers for Emerging Government Policy
2. Ante Harxhi, MD, MBA, Senior Director, Therapeutic Area and Medical Innovation Lead
3. Perry Knight, JD, MHA, Vice President, Law
4. Shanthy Krishnarajah, MPH, MBA/MS, PhD, Senior Director, Scientific Evidence and Policy Research - New Products and IRA
5. Jacqueline Roche, DrPH, Head, Payment and Delivery Reform, Government Affairs and Policy
6. John Schaeffer, MBA, Senior Director, Strategy and Operations for Emerging Government Policy

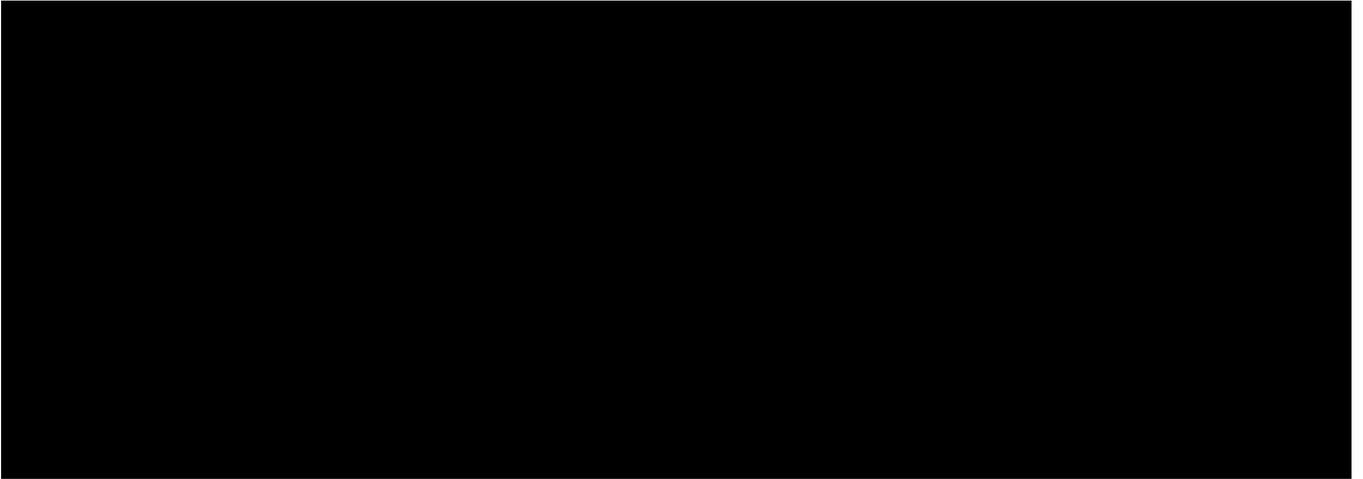
Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- Unmet medical need
- Discuss the clinical rating for NVAf and VTE, including specific questions shared by the Primary Manufacturer
- Medicare beneficiary risk
- Any other considerations that CMS and the Primary Manufacturer would like to discuss

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

- Next steps

Offers/Counteroffers Exchanged:





SUBJECT: Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Janssen Pharms regarding Xarelto on June 24, 2024

Background: Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Janssen Pharms (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Xarelto (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the second negotiation meeting which was requested by CMS and held on June 3, 2024, the Primary Manufacturer had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. The Primary Manufacturer requested a third negotiation meeting and CMS accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the third negotiation meeting, which was held on June 24, 2024 between 1:30 PM ET and 4:00 PM ET.

CMS Attendees:

1. Kaitlin Hunter, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
5. Lee Staley, Representative from the Office of the General Counsel
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

Primary Manufacturer Attendees:

1. Lee Blevins, Senior Director, Strategic Account Managers for Emerging Government Policy
2. Ante Harxhi, MD, MBA, Senior Director, Therapeutic Area and Medical Innovation Lead
3. Perry Knight, JD, MHA, Vice President, Law
4. Shanthi Krishnarajah, MPH, MBA/MS, PhD, Senior Director, Scientific Evidence and Policy Research - New Products and IRA
5. Jacqueline Roche, DrPH, Head, Payment and Delivery Reform, Government Affairs and Policy
6. John Schaeffer, MBA, Senior Director, Strategy and Operations for Emerging Government Policy

Topics: The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:¹

- Introductions and meeting reminders
- Revised offer/counteroffer price discussion
- Any other considerations that CMS and the Primary Manufacturer would like to discuss
- Next steps

¹ Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

Offers/Counteroffers Exchanged:

