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Evolving Healthcare Database Methods to Advance Pharmacoepidemiology

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Evolving Healthcare Database Methods to Advance Pharmacoepidemiology

By

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B.S., Brandeis University, 2016

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An abstract of
A dissertation submitted to the Faculty of the
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Abstract

Evolving Healthcare Database Methods to Advance Pharmacoepidemiology
By Julie Barberio

The field of pharmacoepidemiology often uses real-world data (e.g., electronic health records, health insurance claims) to evaluate safety and effectiveness of products throughout drug development. Scientific and regulatory communities have been hesitant to rely on real-world evidence for regulatory and clinical decision-making due to the potential for epidemiologic biases, which threaten the validity of all observational research. The overarching goal of this dissertation was to evaluate multiple aspects of healthcare database research, assessing how pharmacoepidemiologic methods can be applied to appropriately chosen real-world data sources to inform medication safety and effectiveness.

In Aim 1, we assessed fitness for regulatory purpose of a mother–infant linked cohort in the Japan Medical Data Center claims database for postapproval pregnancy safety studies. Although accurate identification of the complete mother–infant population was possible, limitations of gestational age estimation may impede valid assignment of pregnancy onset and delivery dates as needed to define critical *in utero* exposure windows.

In Aim 2, we evaluated the risks of severe cytopenias in relapsed multiple myeloma patients who received sequential treatment with immunomodulatory agents (IMiDs) versus IMiD-free regimens in the Flatiron Health electronic health records database. Results suggest sequential exposure to IMiDs may increase the risks of severe cytopenias, specifically those related to white blood cells and especially among patients with recent cytopenia histories.

In Aim 3, we investigated the impact of incomplete death information in United States claims data by comparing cardiovascular cumulative risk estimates from models in which death was treated as a censoring event (cause-specific) versus competing event (sub-distribution). Differences in cause-specific versus sub-distribution cumulative risks in the claims-based cohort increased over follow-up time and were largest in the oldest age group, where cardiovascular outcome and mortality risks were the highest. Simulation results demonstrated the differences in cumulative risks to increase in response to doubled and tripled mortality rates.

The results of this dissertation demonstrate the importance of using appropriately chosen real-world databases, high-quality study designs, and rigorous analytic methods to produce valid real-world evidence. With such methods, we can inform trustworthy uses of fit-for-purpose real-world data for regulatory and clinical decision-making, which has important implications for real-world populations (at the practice, provider, and patient levels).

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Table of Contents

Tables

Figures

CHAPTER 1: INTRODUCTION AND BACKGROUND

In the United States, prescription medication use is common, with 46% of individuals reporting recent use of at least one prescription drug.[1] The prevalence of prescription medication use increases with age, such that 85% of adults 60 years or older use at least one prescription drug (most commonly chronic disease medications, such as lipid-lowering drugs, beta-blockers, and antidiabetic drugs), with 35% of this age group using five or more prescription drugs.[1, 2] Prescription medications by definition are bioactive at the doses administered and have been proven to substantially reduce disease burden, improve quality of life, and extend survival time of patients. Approximately one-third of therapeutics approved by the Food and Drug Administration (FDA) are affected by postmarket safety events that were not detected before approval (i.e., new safety information became available after approval that led to either market withdrawal, addition of warnings on the drug's label, or dissemination of safety communications by FDA).[3] Adverse drug events, including adverse drug reactions and errors in medication use, account for 6–7% of hospitalizations in the United States.[4] Patients hospitalized for adverse drug events, who are likely to be older and have more comorbidities, impose substantial financial burden to the healthcare system and are at an increased risk of death.[4, 5] As of 2018, 85 drug products had been withdrawn or removed from the market due to concerns about safety or ineffectiveness of the drug product or component(s) of the drug product that became apparent during the postapproval phase.[6]

FDA requires premarketing clinical evaluation for all new drug products in the United States. Randomized controlled trials are the "gold-standard" assessment for new drug products, given that the comparative analysis and control of extraneous variables allow outcomes to be attributed to the product under study.[7] Important limitations of premarketing clinical trials, however, impede the ability to identify and avoid all subsequent, postmarket adverse events. Although a new drug may demonstrate efficacy (i.e., the ability to treat the indicated condition

under ideal circumstances) in a premarketing clinical trial, its effectiveness (i.e., the ability to treat the indicated condition under the real-world circumstances of usual healthcare practice) demonstrated during the postmarketing phase may vary from efficacy for a number of reasons.[8] For example, clinical trial populations are often restricted to narrow patient groups (e.g., based on geographic area, age, pregnancy status, lack of comorbidities, or lack of use of concomitant medications) and are often healthier than the general patient population, and therefore event rates may not be reflective of those that would occur in the target population for the product under study. Whereas drug administration in premarketing clinical trials follows a strict protocol that is identical for all patients, the unpredictability of real-world physician, pharmacist, and patient use (e.g., due to errors in dose administration, prescription order transcription and dispensing, or adherence to the regimen as prescribed[9]) may also produce discrepancies in the event rates observed in clinical trial versus real-world populations. Furthermore, clinical trial populations are also constricted in terms of both magnitude and duration, which limits the ability to detect rare outcomes and outcomes with long induction periods between drug administration and outcome occurrence. Finally, premarket clinical trials do not typically evaluate polypharmacy and may therefore miss important drug-drug interactions, especially over time as new medications enter the market.[10, 11] These limitations are compounded by the fact that FDA has accelerated drug approvals since the enactment of the Prescription Drug User Fee Act in 1992, since then allowing for the approval of new drug products based on evidence from fewer premarket clinical trials that involve smaller patient groups and are of shorter duration.[12-15] As a result, a greater emphasis has been placed on requirements for pharmaceutical companies to conduct postmarketing studies. Between 2009 and 2018, 91% of the 343 newly FDA-approved drugs had an associated postmarketing requirement at the time of FDA approval, with a median of five requirements per drug.[16] Although about half of such postmarketing agreements required a new clinical trial to be conducted, these postmarket trials are often subject to some of the same limitations as premarket experimental studies.[16]

The field of pharmacoepidemiology addresses some of the limitations of clinical efficacy studies, using epidemiologic methods to study the “use of and effects of drugs” in large, non-randomized, real-world samples.[17] The scope of the field is wide and pertains to the quantification of information unavailable in premarket trials, including drug utilization and prescribing patterns, incidence of adverse and beneficial effects in real-world patient populations, and economic burden related to medication use. Pharmacoepidemiology often employs real-world data (e.g., electronic health records, medical registries, health insurance claims databases) to efficiently evaluate the safety and effectiveness of products throughout the drug development cycle, including at the phase of postmarketing use in the population.[18, 19] Real-world data, which are routinely collected as a part of the healthcare delivery process (i.e., the financing, insurance, and delivery of healthcare) and therefore widely available for a diverse set of patients, can offer cost, resource, and time advantages over conventional clinical trials when it comes to assessing drug products. Additionally, conducting observational studies using real-world data may in some cases be the only ethical way to investigate certain research questions (e.g., medication safety during pregnancy). Evidence derived from real-world data can be useful for detection of postmarket adverse drug events, and may also provide support for primary approval of new medications and approval of supplemental indications for medications.[20, 21]

Concerns do exist in the scientific and regulatory communities, however, regarding the validity of scientific evidence generated from real-world data.[22] Common criticisms about real-world data are generally consistent with the limitations of research using non-randomized data, including the availability of high quality, relevant data suitable to answer regulatory questions of interest, non-randomized allocation of drug products (which is susceptible to bias due to uncontrolled confounding), and missing information (especially as it relates to outcome and competing event data, which has implications for event risk estimation).[23-26] The utility of

evidence generated from real-world data (i.e., real-world evidence) relies on the validity of the data and on the quality and suitability of the design and analysis methods implemented. Research that lacks internal validity may result in false positives regarding effectiveness or false negatives regarding safety, both of which have detrimental effects on real-world patient populations by either denying them the effective care that they need or by needlessly putting them at risk for adverse events. The passing of the 21st Century Cures Act in December 2016 required FDA to evaluate the role of real-world data in supporting regulatory decision-making, which has important implications for the pharmaceutical industry and for clinical practice as well.[27] Each aim of this dissertation will address a distinct methodological challenge facing epidemiologists in the pharmaceutical setting with regards to evaluating real-world database fitness for regulatory purpose (Aim 1), using real-world data to evaluate comparative safety of complex, non-randomized treatment regimens (Aim 2), and understanding the impact of missing death information on real-world evidence (Aim 3). As we will demonstrate, choice of a suitable real-world database, coupled with implementation of high-quality study design techniques and analytical methods, can offset the epidemiologic biases that threaten the validity of observational pharmacoepidemiology studies using real-world data.

Overarching Goal and Specific Aims

The overarching goal of this dissertation was to evaluate the validity of aspects of healthcare database research in the pharmaceutical industry and to assess how pharmacoepidemiologic methods can be applied to appropriately chosen real-world data sources to deliver influential and valid real-world-based evidence regarding medication safety and effectiveness. This goal was addressed by the following specific aims:

1. Use the Duke-Margolis framework to assess whether a linked cohort of mothers and infants in a Japanese claims database is fit for purpose within the regulatory context of

estimating infant outcomes associated with *in utero* exposure to marketed medications.

2. Evaluate the risk of developing cytopenias in relapsed multiple myeloma patients who received sequential treatment with immunomodulatory drugs as compared with those on an immunomodulatory drug-free regimen (within 3, 6, and 12 months of treatment initiation).
3. Investigate the influence of specifying death as a health plan disenrollment censoring reason versus specifying death as a distinct competing event on cardiovascular cumulative risk estimates at early and late follow-up periods among new users of a medication under variations of population characteristics.

Aim 1 served to demonstrate the assessment of real-world data fitness for regulatory purpose and inform the types of pregnancy studies (which could be tailored to various birth outcomes and *in utero* medication exposures) that may be validly conducted using a mother–infant linked population in a Japanese claims database. Aim 2 served to demonstrate how study design techniques and statistical modeling can be used to address comparative safety questions in the presence of confounding bias due to complex, non-randomized prescribing patterns and inform clinical decisions regarding regimen prescribing for relapsed multiple myeloma patients. Aim 3 served to allow future researchers to predict the impact of not specifying death as a competing risk, because of missing information on death, on the validity of cumulative risk estimates based on characteristics of their patient population (particularly age and mortality rate). Overall, by demonstrating the situations in which real-world data may be used to generate valid answers to comparative safety and effectiveness questions with important implications for real-world populations (at the practice, provider, and patient levels), this dissertation serves to promote trust in fit-for-purpose real-world data.

CHAPTER 2: CHARACTERIZING FIT-FOR-PURPOSE REAL-WORLD DATA: AN ASSESSMENT OF A MOTHER–INFANT LINKAGE IN THE JAPAN MEDICAL DATA CENTER CLAIMS DATABASE

Abstract

Introduction: The potential for administrative databases to inform medication safety during pregnancy has been increasingly recognized. Mother–infant linkages in databases enable evaluation of infant outcomes. However, database availability, which has increased in recent years, does not inherently dictate suitability to generate evidence to inform regulatory decision making (whether the data are “fit for regulatory purpose”), emphasizing the importance of fit-for-purpose real-world data evaluation.

Objective: Use the Duke-Margolis framework to assess whether a linked cohort of mothers and infants in the Japan Medical Data Center (JMDC) claims database is fit for purpose within the regulatory context of estimating infant outcomes associated with *in utero* exposure to marketed medications.

Methods: The Duke-Margolis framework considers whether a database is fit for regulatory purpose based on relevancy and quality. Relevancy relates to capacity to answer the research question, in terms of availability of critical data fields and a sufficiently sized, representative population. Quality relates to ability to validly answer the research question, in terms of data completeness, accuracy, and transparency. To assess these considerations, we estimated the number of pregnancies that could be linked to an infant among females ages 12–55 in the JMDC between January 2005 and March 2022 using two different linkage approaches. Descriptive characteristics were examined.

Results: In terms of relevancy, we determined that critical data fields (maternal medication exposures, infant major congenital malformations, covariates) were available. Family identification codes permitted patient-level mother–infant linkage. 385,295 total valid mother–

infant pairs were identified, representing about 2% of live births in Japan during the study period. About 41,000 congenital malformations were observed among these pairs. 57% of pairs involved a mother with continuous enrollment during pregnancy and 86% had at least one year of infant follow-up; 49% met both pregnancy and follow-up continuous enrollment. Comparison to publicly available data from Japan suggested preterm births were under-recorded (3.6% versus 5.6%) in this population. Overall congenital malformations were over-represented (10.8% versus 5.3%), yet the prevalence of each specific malformation subcategories was representative of rates in the general population. Maternal characteristics appeared mostly consistent with the population of same-aged females in Japan.

In terms of quality, our methods were expected to accurately identify the complete set of mothers and infants in the JMDC enrolled in a shared health insurance plan. Females with evidence of a live birth delivery had a linkage rate of about 50%, which aligns with expectations of infant insurance coverage under the mother's, versus another parent's, plan. Cross-tabulation of values indicated for the relationship of the "mother" and "infant" to the insurance holder allowed for confirmation of plausible biologic mother–infant pairs. However, the completeness and accuracy of gestational age information was limited given the lack of live birth delivery codes for 60% of the cohort coupled with suppression of infant birth dates and inaccessibility of International Classification of Diseases codes with fifth level digits (where gestational week information would have been available) in the database.

Conclusions: Results suggest the JMDC may be well-suited for descriptive studies of pregnant people in Japan (e.g., comorbidities, medication usage). More work is needed to identify a method to assign pregnancy onset and delivery dates so that *in utero* exposure windows can be defined more precisely as needed for many regulatory postapproval pregnancy safety studies.

Introduction

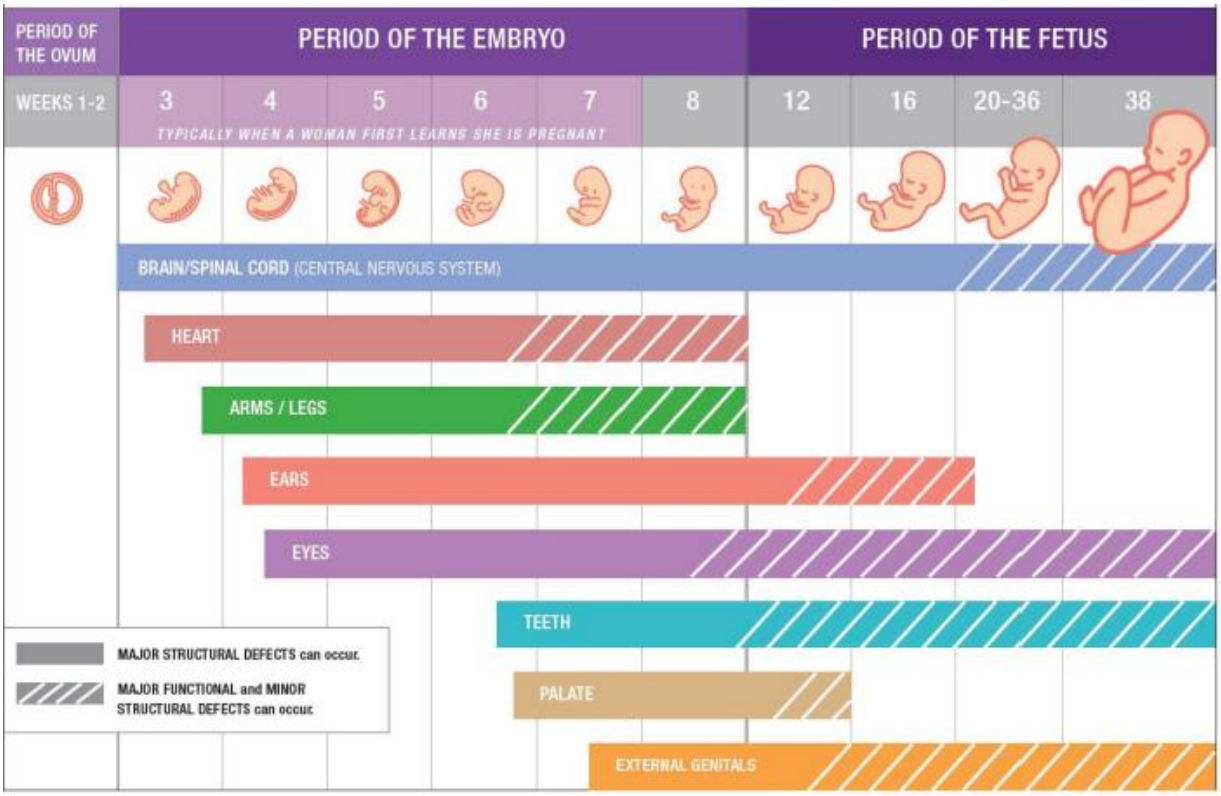
Exclusion of pregnant people from clinical trials precludes the premarket availability of information regarding medication safety during pregnancy, thus postapproval safety studies are generally required by the United States Food and Drug Administration (FDA) when a new drug product is expected to be used among persons of childbearing age.[28, 29] The requirement for postapproval safety investigation has conventionally been completed via the establishment of pregnancy exposure registries (typically sponsored by a single pharmaceutical company), but regulatory agencies have been demonstrating increasing interest in database approaches.[30] Pharmacoepidemiology often employs real-world data (e.g., electronic health records, medical registries, health insurance claims databases) to efficiently evaluate the safety and effectiveness of products throughout the drug development cycle, including at the phase of postmarketing use in the population.[18, 19] Throughout, we use the inclusive terminology "pregnant people" to acknowledge that many people have uteri and can become pregnant (e.g., women, people who are non-binary, people who are transmasculine).[31]

Administrative healthcare databases are an important source of pharmacoepidemiologic data for postapproval pregnancy safety studies. Designing a pregnancy-related cohort in a healthcare database according to the components of a hypothetical randomized clinical trial allows for this resource to be used for causal inference regarding medication safety during pregnancy.[32-34] There are two key components of target trial emulation in pregnancy safety research: mother–infant linkages and pregnancy timing.[35] Healthcare claims, which are collected for billing purposes, do not inherently indicate correspondence between mothers and their infants or pregnancy timing (e.g., estimated dates of conception and delivery) and therefore this information must be reconstructed by researchers who use the database.[36-46] First, linkage of pregnant people and their infants is required to emulate a pregnancy target trial as both exposure status and infant outcome evaluation must occur to study the

multigenerational impact of drug exposures during pregnancy on infant outcomes.[35] Without valid linkage of pregnant people and their infants, the pregnant person's record in isolation will not necessarily contain information regarding infant outcomes and the infant's record in isolation will not contain information regarding maternal medication use during pregnancy. It is important to note that such linked populations in administrative claims databases are usually restricted to those with female gender codes in an attempt to identify the population with uteri who can become pregnant, given that this information is otherwise not directly available. This population is not necessarily restricted to cisgender females and we therefore recognize use of the binary "female" versus "male" gender classification to be suboptimal. Furthermore, while populations beyond cisgender females may identify as mothers, we acknowledge the term "mother" in itself to be gendered and non-inclusive.[31]

Second, pregnancy timing information is required for a pregnancy target trial emulation because in a hypothetical randomized trial of pregnant people, trial enrollment and subsequent exposure randomization would need to occur at a specific gestational age, the specifics of which would depend on the outcome of interest.[35] This is due to the fact that specific types of congenital malformations arise at different stages of fetal development (**Figure 1**).[47] For example, as development of the heart occurs during the first trimester, it is during this critical period that cardiac malformations may originate; exposures occurring later in pregnancy are irrelevant for the study of cardiac malformations (but may be important for abnormalities of other body systems).

Figure 1. Sensitive periods of fetal development and related major structural and functional defects



From MotherToBaby (2021)[47]

Population-based, prospectively collected administrative healthcare databases allow researchers to construct large, diverse pregnancy cohorts with accurate prescription information, enabling the study of rare pregnancy outcomes while avoiding recall bias.[19, 48-50] This data resource has several advantages over medication-based pregnancy registries, which often suffer from difficulties with representative enrollment (due to the typical reliance on voluntary participation), long-term retention and loss to follow-up, and lack of an appropriate comparator group.[51, 52] Furthermore, pregnant people are often not enrolled in pregnancy registries until later in pregnancy, thereby missing spontaneous abortions or stillbirths that may have occurred earlier in gestation and potentially resulting in a left truncated cohort, depending on the research question of interest.[50] The use of pre-existing, routinely collected healthcare claims may address these concerns to some extent. Key drawbacks of using healthcare claims to examine medication safety during pregnancy are consistent with the general limitations of

research based on automated medical and prescription claims, such as the incomplete capture of key lifestyle factors (e.g., alcohol use, tobacco use, obesity, folate consumption), the lack of information on actual prescription medication consumption, and the possibility of loss to follow-up of both pregnant individuals and infants due to changes in health plan enrollment.[46]

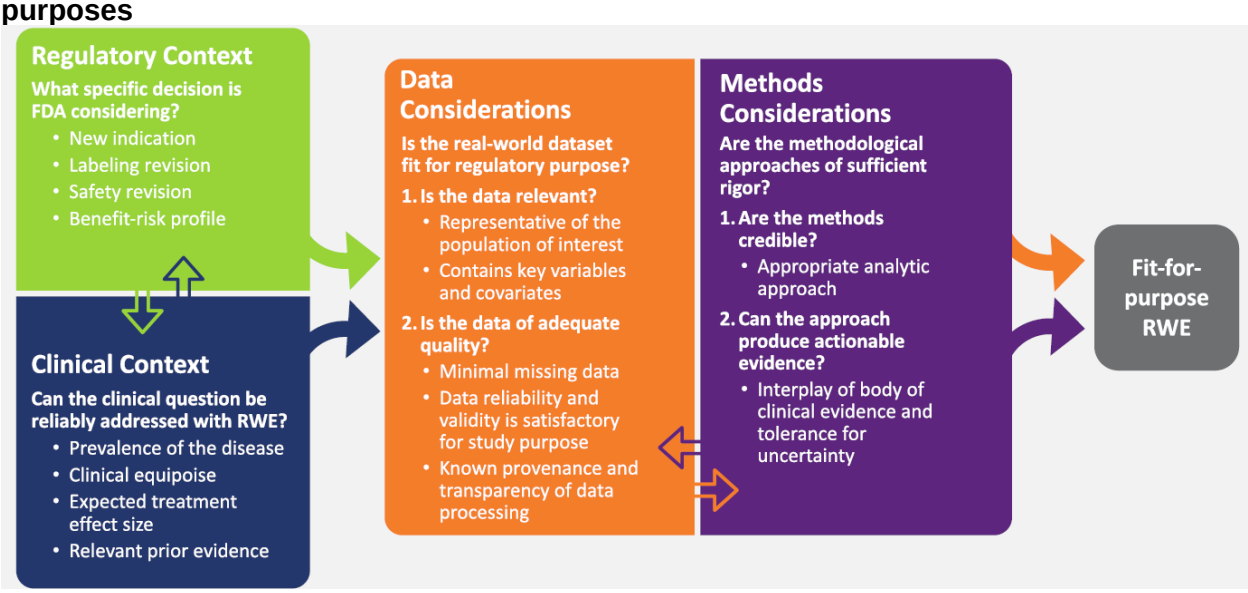
Although the availability of large, detailed real-world databases (i.e., databases that are routinely collected as a part of the healthcare delivery process; e.g., health insurance claims, electronic health records) has continued to increase in the past decade, real-world data availability alone does not inherently dictate suitability to generate real-world evidence intended to inform regulatory decision-making. The passing of the 21st Century Cures Act in December 2016 required the US FDA to evaluate the role of real-world data in supporting regulatory decision-making, which has important implications for the pharmaceutical industry and for clinical practice as well.[27] In partial fulfillment of this requirement, the FDA released a framework on real-world evidence in December 2018.[24] This framework introduced a three-part approach, which considers:

> *"(1) whether the real-world data are fit for use, (2) whether the study design can provide adequate scientific evidence to answer or help answer the regulatory question, and (3) whether the study conduct meets FDA regulatory requirements."*[24]

Similar real-world evidence frameworks have also been released by regulatory agencies in Canada, Europe, and Asia.[53, 54] In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has released and updated several guidelines in recent years to promote use of real-world data throughout the drug life cycle, with a particular focus on assuring data reliability in postmarketing safety studies.[55, 56] Understanding whether real-world data generated from the financing, insurance, and delivery of healthcare may be "meaningfully, validly, and transparently" used to answer a real-world safety and effectiveness question of regulatory

interest, henceforth referred to as “fit-for-purpose real-world data,” is an important prerequisite for using the data to inform decision-making by patients, physicians, practices, and regulatory agencies.[25] To this end, the Duke-Margolis Center for Health Policy, in collaboration with FDA, has developed a framework for evaluating fitness for purpose of real-world evidence for regulatory decision-making.[25, 26] The framework recommends evaluating whether real-world evidence is fit for regulatory purpose by considering four key perspectives: (1) the regulatory question of interest, (2) the clinical context, (3) considerations of the data, including the availability of relevant, high-quality data, and (4) the application of sufficient methodological approaches (**Figure 2**).[25]

Figure 2. Considerations for generating real-world evidence that is fit for regulatory purposes



Daniel et al (2018). Characterizing Real-World Data Quality and Relevancy for Regulatory Purposes.

The objective of this analysis was to apply the Duke-Margolis framework, focusing particularly on the data considerations (**Figure 3**), to evaluate the fitness for purpose of a linked cohort of mothers and their infants in the health insurance claims database maintained by the Japan Medical Data Center (JMDC), within the specific regulatory context of estimating infant major congenital malformations associated with *in utero* exposure to marketed medications.

Figure 3. Considerations for whether real-world data are fit for regulatory purposes

Daniel et al (2018). Characterizing Real-World Data Quality and Relevancy for Regulatory Purposes.

The FDA has released guidelines regarding the use of real-world data to complement data obtained from pregnancy registries, specifically stating that database choice needs to consider "methods used to identify pregnancies, estimates of conception and gestational age, linkage to offspring records, and ascertainment and validation of pregnancy and birth outcomes."[57] Furthermore, the FDA has committed to establishing standard practices for use of real-world data to assess pregnancy safety by 2027.[58] The PMDA has recently expressed intentions to improve existing registry-based infrastructure for pregnancy safety research, but has yet to comment on the use of real-world data in this setting.[59, 60] Although claims-based mother–infant linkages have been established in the US, there is value in adding and evaluating this resource in Japan due to the differences between Japan and the US in terms of standards of obstetric care, prescription medication recommendations in pregnancy, and the healthcare systems.[61-63] The results of this fit-for-purpose real-world data evaluation will be used to inform whether internally valid pregnancy surveillance studies (which could be tailored to various birth outcomes associated with *in utero* exposure to specific medications) may be conducted using a mother–infant linked population in the JMDC claims database, which has implications for the dissemination of research results in practice.

Methods

Study Population

The data source for this analysis was the health insurance claims database maintained by the Japan Medical Data Center (JMDC). The JMDC is Japan's largest claims database, making it a strong choice of real-world data to efficiently evaluate the safety and effectiveness of drug products in the Japanese population.[64] The JMDC is compiled from over 1,400 private companies that belong to the Health Insurance Association, one of five payer organizations of the Japanese National Health Insurance System. All citizens of Japan are covered by the National Health Insurance System, provided either through their employer or through the government. All infants in Japan are enrolled in the National Health Insurance System within one month of birth. The national insurance covers most medical services, including drugs, with the exception of over-the-counter drugs, vaccinations, and cosmetic surgeries. A fixed fee is used for each medical service across the country, and co-payment ratios are defined by age groups (e.g., 30% of treatment cost for individuals ages 6–69 years). Japan does not use a primary care physician system; citizens are free to visit any medical facility at any time, with no referrals needed. The JMDC claims database includes all inpatient, outpatient, and pharmacy claims received from multiple insurers in Japan. Unique patient identifiers allow each patient to be tracked longitudinally, given that they are covered by a consistent payer. The claims contain diagnoses (classified according to the International Classification of Diseases, 10th Revision [ICD-10]), medical procedures, and prescribed medications, all with dates available.[45]

Linkage of mothers and infants as required by the target trial framework is possible, assuming that the infant is a dependent on a shared insurance plan with the mother, via family identification variables assigned in the JMDC claims database to the insured individual and all of their dependents. In the Japanese National Health Insurance System, dependents may be any family member who is financially supported by the insured individual. This group is not limited to

the spouse and child(ren), and may additionally include other blood relatives (e.g., parents, siblings, grandparents), in-laws, or stepchildren of the insured individual.

Critical pregnancy timing as needed for pregnancy target trial emulation may be estimated based on claims representing diagnoses and procedures at delivery, as well as those that occur at the beginning of and throughout a pregnancy.[36-45] Delivery in itself is not necessarily always covered by the Japanese National Health Insurance System and therefore a delivery that does not require any surgical procedures or medications covered by the health insurance would not appear in Japanese claims. As a result, it is expected that the JMDC claims database will present an incomplete report of deliveries, particularly over-representing complicated deliveries requiring medical intervention. Furthermore, the National Health Insurance does not cover pregnancy confirmation tests or prenatal health visits, although these costs are subsidized by the government. Missing delivery and pregnancy care information is expected to impede the ability to estimate pregnancy timing in this database, which is vital for defining *in utero* medication exposure windows in pregnancy safety research. This missing information therefore provides an incomplete representation of interactions with the health system during pregnancy.

The fitness for purpose of the JMDC claims database as a source of real-world data for the study of medication safety during pregnancy has not been evaluated. Ishikawa et al. recently created a mother–infant linked cohort in the JMDC claims database, but did not comment on the expected validity of the paired mothers and infants nor describe how various steps of their linkage process may have affected the generalizability of the cohort relative to the target population of all mothers and liveborn infants in the Japan.[44, 45] For example, their requirement for continuous enrollment in the health plan in the year before the birth of the infant resulted in the exclusion of 36% of mother–infant pairs (approximately 27,500) and their inability to estimate pregnancy timing resulted in the exclusion of an additional 15% of mother–infant pairs (approximately 7,300). Furthermore, as nearly 1.7 million females in the JMDC (96%) remained

unlinked by Ishikawa et al., distinguishing between females without a pregnancy during the study period (not part of the target population of mothers and liveborn infants in Japan), females who experienced a pregnancy that ended in a fetal death (not part of the target population), and females with liveborn infants that could not be linked in the database (part of the target population) is an important prerequisite for understanding the fitness for purpose of the JMDC claims database for generating pregnancy-related real-world evidence. Finally, the number of infants in the JMDC claims database that remained unlinked by Ishikawa et al. (i.e., because their mother is covered by a different insurer) is unknown, which is also vital for understanding how well the matched infants represent the totality of infants covered by the JMDC. The present analysis will therefore expand upon previously published mother–infant cohorts using the JMDC claims database by adding a formal evaluation of database fitness for regulatory purposes, as outlined by the Duke-Margolis framework.[25]

Data Considerations

We used the Duke-Margolis framework to evaluate the fitness for purpose of a mother–infant linkage in the JMDC claims database. The Duke-Margolis framework states that considerations for whether a source of real-world data is fit for regulatory decision-making, within a given context, involves the dimensions of (1) data relevancy and (2) data quality. The relevancy of a given real-world database relates to the capacity of the database to answer the regulatory research question, in terms of the availability of critical data fields and a sufficiently sized, representative population. This evaluation relates to the potential for selection bias in the study population. The quality of a real-world database relates to the ability of the data source to accurately, reliably, and transparently answer the regulatory question of interest. This evaluation relates to the potential for information bias in the study processes. Our analyses considered the relevancy of the JMDC claims database to be used to answer regulatory questions related to medication safety during pregnancy, as well as the quality of information available for (A) the

formation of the mother–infant matches and (B) the estimation of the gestational period, as required for pregnancy safety research.

Statistical Analyses

We performed two linkage methods to generate various descriptive statistics (frequencies, distributions, and completeness of data fields) that allowed us to assess the data relevancy and quality dimensions. The analyses were conducted as follows: (1) performed Linkage Method A to assess number of successful linkages relative to the estimated number of unique pregnancy episodes identifiable in the JMDC database, (2) performed Linkage Method B to assess number of successful linkages relative to all infants in the JMDC database, (3) examined the presence of pregnancy or delivery codes among successful linkages from Linkage Method B, (4) assessed validity of mother–infant linkages from Linkage Method B, (5) assessed annual valid pairs available from Linkage Methods A and B, and (6) described characteristics of the valid pairs linked via Linkage Method B, including both female characteristics and infant characteristics.

Linkage Method A first identified potential pregnancy episodes, according to active pregnancy and delivery codes, and then determined the proportions that were successfully linked to infants to inform expected completeness of mother–infant pairs in the JMDC database. Active pregnancy codes were defined as diagnosis codes that indicated a person to be presently in a pregnant state and delivery codes were defined as diagnosis codes that indicated occurrence of a live birth delivery.[65] All codes were defined according to ICD-10 (**Table 1**).

Table 1. Claims-based definitions for active pregnancy and live birth delivery episodes

Category	ICD-10 Diagnosis Codes
Active Pregnancy	O100–O104, O11, O120–O121, O13–O16, O20, O210–O212, O22 (not O228), O23 (not O233), O24 (not O243, O248), O25, O26 (not O269), O29 (not O294, O295, O298), O30 (not O308), O310 (not O313), O32, O33 (not O334, O338), O34 (not O345, O347), O350, O351, O353, O358, O359, O36, (not O367, O369), O40, O41, O42, O43, O441, O450, O459, O469, O47, O48, P07, Z33, Z349
Live Birth Delivery	O601, O603, O611, O619, O62 (not O628), O630, O631, O639, O64 (not O645, O649), O651, O654, O655, O66 (not O664–O668), O679, O68, O68, O69 (not O691), O70 (not O704), O71 (not O718), O72, O73, O742, O743, O744, O749, O75 (not O754, O759), O80 (not O808), O81 (not O812), O820, O821, O829, O830, O831, O839, O840, O842, O849, O85, O86 (not O868), O87, O88 (not O888), Z380–Z383

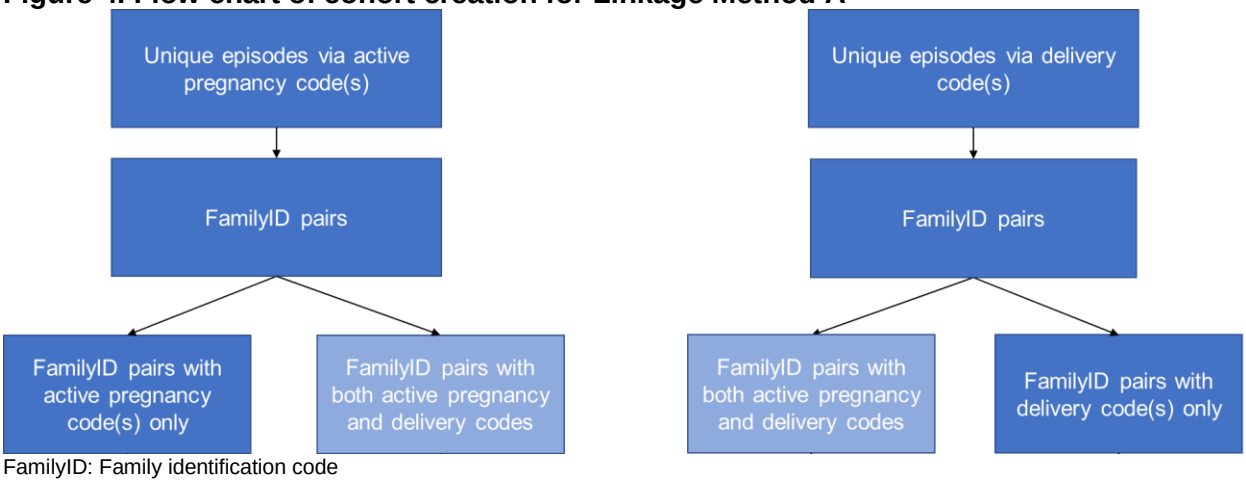
ICD-10: International Classification of Diseases, Tenth Revision

Linkage Method A was conducted as follows (**Figure 4**):

1. Identified all females ages 12–55 between January 2005 and March 2022 with any code from the active pregnancy code list. Restriction to those with female gender was done in an attempt to identify the population with uteri who can become pregnant. This population is not necessarily restricted to cisgender females and we recognize this binary gender classification to be suboptimal.
    i. For each female, started from the first date of the pregnancy code and set as the first pregnancy start date.
    ii. Continued checking if the next pregnancy code date was within 294 days (estimated maximum end date); if not, set the date as a new pregnancy episode start date.
    iii. Repeated step 1i–ii, created a table for each female with each pregnancy episode start and end date.
    iv. Matched step 1iii table to infants (dependent members whose enrollment start month/year is the same as their birth month/year) with same family identification code. Required infant date of birth (set as 15th day of birth month) to be within pregnant episode start date and end date. A single pregnancy episode may have had multiple births and therefore a single mother may have had multiple infant pair matches (e.g., twins).

2. Identified all females ages 12–55 with any code from the delivery code list.
    i. For each female, started from the first date of the delivery code and set as the delivery date (pregnancy end date).
    ii. Continued checking if the next delivery code date is within 168 days; if not, set the date as a new delivery episode date.
    iii. Repeated step 2i–ii, created a table for each female with each delivery episode date.
    iv. Matched step 2iii table to infants (dependent members whose enrollment start month/year is the same as their birth month/year) with same family identification code. Required infant date of birth (set as 15th day of birth month) to be within ±60 days of the delivery date. A single pregnancy episode may have had multiple births and therefore multiple pairs (e.g., twins).
3. Of the family identification code pairs created in steps 1iv and 2iv, classified into mutually exclusive groups:
    i. Pairs identified in both 1iv and 2iv.
    ii. Pairs identified in only 1iv (and not 2iv).
    iii. Pairs identified in only 2iv (and not 1iv).

Figure 4. Flow chart of cohort creation for Linkage Method A

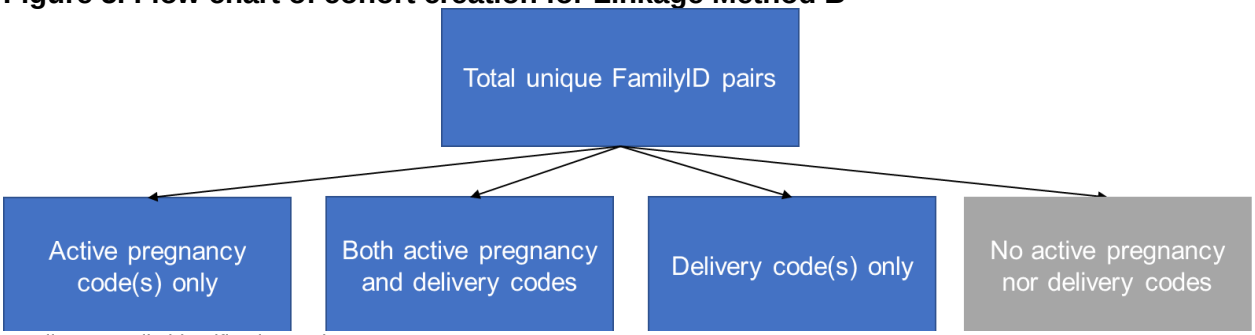


FamilyID: Family identification code

The process of Linkage Method B was opposite that of Linkage Method A; Linkage Method B began by identifying mother–infant pairs and then examined the prevalence of pregnancy and delivery codes among the pairs. Linkage Method B informed the proportion of infants in the JMDC that successfully matched with a mother, as well as the expected accuracy and completeness of delivery and gestational age information (which would rely on pregnancy and delivery codes). Specifically, Linkage Method B was conducted as follows (**Figure 5**):

1. Identified all females ages 12–55 between January 2005 and March 2022 who had a matching family identification code to an infant (dependent member whose enrollment start month/year is the same as their birth month/year). Allowed females to match to multiple unique infants (e.g., siblings, multiples).
2. Set delivery date as the 15th day of the infant birth month.
3. Of the family identification code pairs identified, determined how many would have been identified based on presence of the following code types:
    i. Active pregnancy code(s). Maternal records included at least one code from the active pregnancy code list within the 294 days before the delivery date.
    ii. Completed pregnancy outcome code(s). Maternal records included at least one code from the delivery-related code list in ±60 days from the delivery date.
4. Of those classified in 3i and 3ii, classified into mutually exclusive groups:
    i. Pairs who met both 3i and 3ii.
    ii. Pairs who met only 3i (and not 3ii).
    iii. Pairs who met only 3ii (and not 3i).
    iv. Pairs who met neither 3i nor 3ii.

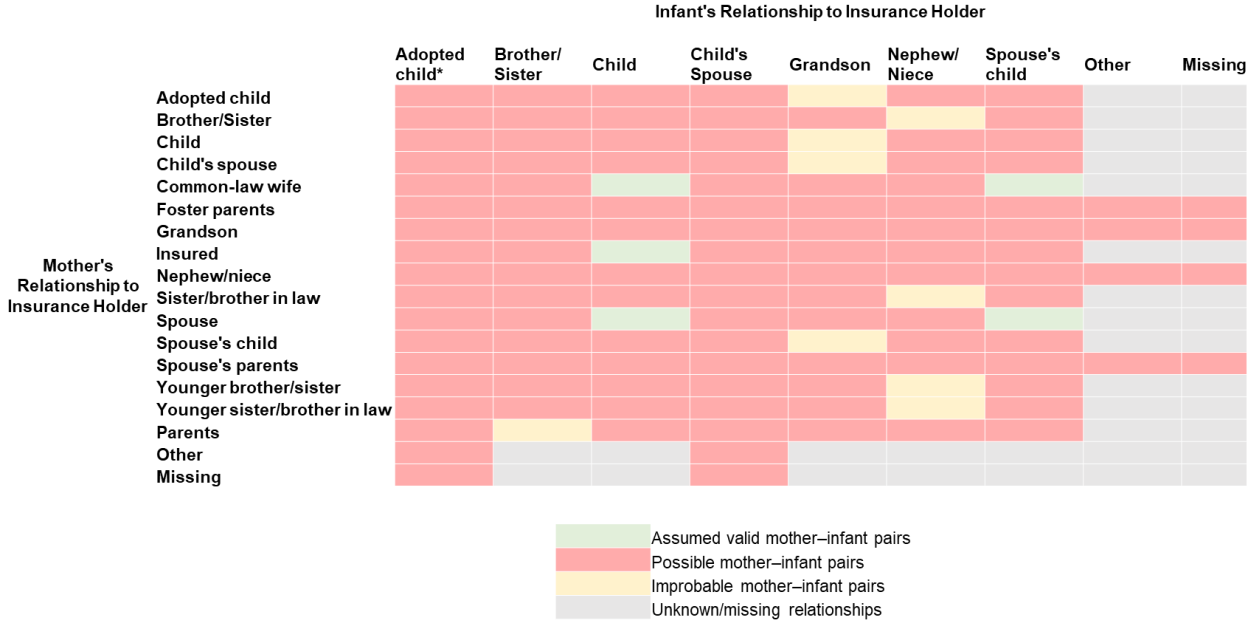
Figure 5. Flow chart of cohort creation for Linkage Method B



FamilyID: Family identification code

Next, using the matched pairs created in Linkage Method B, we evaluated the relationship that the matched "mother" and "infant" both had to the insurance holder to inform validity of the assumed mother–infant relationships between pairings of females age 12–55 years with infants who shared a family identification code. In the JMDC claims database, a unique family identification variable is assigned to the insured individual and all of their dependents, regardless of relationship (which may include any family member who is financially supported by the insured individual and is not limited to the spouse and children). The JMDC enrollment data includes a separate variable that indicates an individual's relationship to the insurance holder. By cross-referencing the values indicated for the "mother" and the "infant," we were able to understand whether plausible mother–infant pairs were formed. Our categorization scheme for the assumed validity of mother–infant pairings, based on their relationships to the insurance holder, is shown in **Figure 6**. It is worth noting that we assumed incestuous mother–infant relationships, although biologically possible, to be implausible (e.g., if both members of the pair were indicated as a "child" of the insurance holder, it is biologically possible that the male insurance holder impregnated his own daughter. It is more likely, however, that this represents a sibling pair that was linked as a mother–infant pair by our algorithm in error).

Figure 6. Categorization of assumed validity of mother–infant pairings based on both individual's relationship to the insurance holder



*Although some of the "adopted child" infant relationships could be valid relationships between mother and child, these are not valid mother–infant pairs for the purposes of studying *in utero* exposures.

Relationships considered to be confident biologic mother–infant pairs were those in which the infant was listed as the child of the insurance holder while the mother was either the insurance holder or the spouse (including common-law spouse) of the insurance holder, or the infant was listed as the insurance holder's spouse's child while the mother was listed as the spouse. Several relationships were considered to be "possible" mother–infant pairs, defined as pairs in which the mother and the infant possessed relationships to the insurance holder that could qualify them as a biologic mother–infant pair, but without additional family tree information we lacked the ability to confirm a mother–infant relationship (e.g., the mother is the sister of the insurance holder and the infant is the nephew/niece of the insurance holder).

In an attempt to improve validity of the mother–infant linkages, two exclusions were made before proceeding with evaluation of descriptive characteristics. First, we excluded invalid/inconclusive pairings based on the mother's and infant's relationships to the insurance holder. We excluded all pairs whose relationships to the insurance holder qualified them as

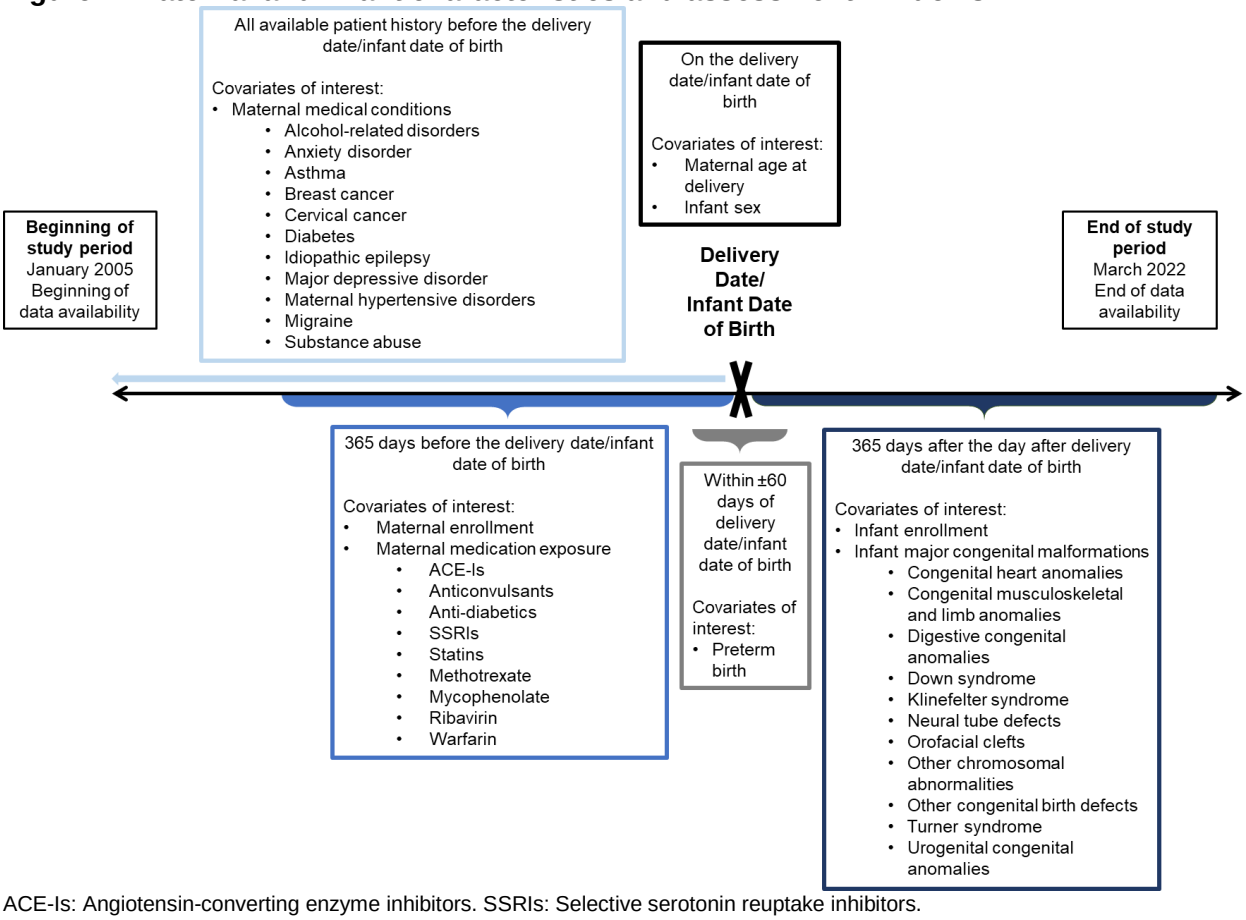
either confidently not mother–infant pairs or pairs of unknown validity. We also excluded possible mother–infant pairs for which pregnancy and/or delivery codes were absent, given the lack of evidence for validity of these pairs. We acknowledge that retaining possible pairs with pregnancy or delivery codes could have resulted in inclusion of invalid pairs, but suspect that the overlap of pregnancy/delivery codes with the birth of the infant supports a biologic mother–infant relationship. We also excluded infants who successfully matched with more than one mother, which could have occurred for infants involved in “possible” mother–infant pairs.

Using the matched, valid pairs created in the two linkage methods, we created estimates of the number of annual births according to (1) all matched pairs from Linkage Method A, (2) all pairs from Linkage Method B, regardless of pregnancy and/or delivery codes and (2) only the pairs from Linkage Method B with pregnancy and/or delivery codes.

Finally, using the matched, valid pairs created in Linkage Method B, we examined descriptive characteristics of the mother–infant linked cohort for (1) all pairs and (2) only those pairs with pregnancy and/or delivery codes. We chose to proceed with the Linkage Method B cohort for this analysis given that this method allows for direct identification of pairs of mothers and liveborn infants without reliance on the presence of diagnosis codes during pregnancy or at delivery. Linkage Method B is therefore expected to result in a more complete representation of the population of mothers and liveborn infants in the JMDC claims database, compared to Linkage Method A, due to the fact that prenatal care and delivery hospitalizations may not necessarily generate healthcare claims in Japan. The assessment windows for the various characteristics of interest are displayed in **Figure 7**. Maternal medical conditions were examined on maternal records according to available patient history before the delivery date and maternal medication exposures were examined on maternal records in the year before the delivery date. Maternal characteristics were assessed once per unique female. For females with more than one linked infant, a single delivery date was randomly selected to define the maternal covariate

assessment period. Infant major congenital malformations were examined on infant records in the year following the delivery date. Preterm birth was assessed on both maternal and infant records within the 60 days before or after the delivery date.

Figure 7. Maternal and infant characteristics and assessment windows



ACE-Is: Angiotensin-converting enzyme inhibitors. SSRIs: Selective serotonin reuptake inhibitors.

These characteristics were defined using ICD-10 algorithms from the Global Burden of Disease (GBD) descriptive epidemiology study, which are provided by the Global Health Data Exchange (GHDx; **Table 2**).[66, 67] Medication exposures were defined according to the Anatomical Therapeutic Chemical (ATC) classification system from the World Health Organization (WHO) (**Table 3**).

Table 2. Claims-based definitions for maternal medical conditions and infant major congenital malformations

Category	ICD-10 Diagnosis Codes
Female Medical Conditions	
Alcohol use disorders	E244, F100– F107, G312, G621, R780
Anxiety disorders	F40 (not F408), F41 (not F413), F420, F421, F429, F43 (not F438), F440 (not F443), F930
Asthma	J45, J46
Breast cancer	C50, Z123
Cervical cancer	C53
Diabetes	E10 (not E102, E108), E11 (not E112, E118), E12, E13 (not E132, E138), E14 (not E142, E147, E148), R730, R739
Epilepsy	G40, G41 (not G418)
Major depressive disorder	F32, F33 (not F338)
Maternal hypertensive disorders	O10 (not O109), O11, O120, O121, O13, O14, O15, O16
Migraine	G430
Substance use disorders	E244, F100– F107, F112, F120, F122, F127, F130, F131, F132, F140, F142, F150, F151, F152, F155, F157, F160, F161, F162, F170, F172, F180, F181, F182, F19 (not F194, F198), G312, G621, P961, R780, R782, R786, R787
Infant Major Congenital Malformations	
Congenital heart anomalies	Q20 (not Q209), Q21, Q22 (not Q229), Q23 (not Q239), Q24, Q25, Q26, Q27, Q28 (not Q289)
Congenital musculoskeletal and limb anomalies	Q650, Q651, Q652, Q658, Q659, Q660, Q661, Q680, Q681, Q682, Q688, Q69, Q70, Q711, Q713, Q714, Q715, Q716, Q719, Q721, Q723, Q724, Q727, Q729, Q730, Q731, Q738, Q740, Q741, Q742, Q743, Q749, Q750, Q755, Q759, Q761, Q762, Q764, Q769, Q77, Q78, Q798, Q799
Digestive congenital anomalies	Q380, Q383, Q384, Q386, Q387, Q388, Q39, Q400–Q403, Q410 (not Q418), Q421, Q423, Q429, Q43 (not Q431), Q44, Q450–Q458, Q790–Q795
Down syndrome	Q90
Klinefelter syndrome	Q980, Q981, Q984
Neural tube defects	Q00, Q01, Q054–Q059, Q070
Orofacial clefts	Q35, Q36, Q37, Q37
Other chromosomal abnormalities	Q748, Q751, Q754, Q758, Q796, Q87, Q91, Q922, Q923, Q926, Q928, Q929, Q932–Q935, Q938, Q939, Q970, Q971, Q99
Other congenital birth defects	G712, Q02, Q03, Q04, Q06 (not Q063), Q07, Q10, Q11, Q12, Q13, Q14, Q15, Q17, Q18 (not Q187), Q270, Q30, Q31, Q32, Q33 (not Q335), Q34, Q381, Q382, Q385, Q430, Q459, Q662–Q668, Q680, Q683, Q684, Q685, Q740, Q752, Q753, Q760, Q765, Q766, Q767, Q80, Q810, Q811, Q812, Q523, Q525, Q53, Q552, Q633, Q653–Q656, Q818, Q819, Q82, Q83 (not Q830), Q84, Q85, Q860, Q890–Q898
Turner syndrome	Q960, Q963, Q964, Q969
Urogenital congenital anomalies	P960, Q50, Q51 (not Q515–Q517), Q520–Q522, Q524, Q526, Q527, Q529, Q54 (not Q544), Q55 (not Q558), Q560–Q562, Q640, Q641
Delivery Characteristics	
Preterm birth	P072, P073

ICD-10: International Classification of Diseases, Tenth Revision

Table 3. Claims-based definitions for maternal medication exposures

Category	WHO ATC Code
ACE-Is	C09AA, C09AA01, C09AA02, C09AA03, C09AA04, C09AA06, C09AA07, C09AA08, C09AA10, C09AA12, C09AA14, C09AA16
Anticonvulsants	B05XA05, N02BG11, N03AA03, N03AB01, N03AB02, N03AB05, N03AB52, N03AC02, N03AD01, N03AE, N03AE01, N03AF01, N03AF03, N03AG01, N03AG04, N03AX03, N03AX09, N03AX11, N03AX12, N03AX13, N03AX14, N03AX15, N03AX16, N03AX17, N03AX18, N03AX22, N05BA01, N05BA06, N05BA09
Anti-diabetics	A10AB01, A10AB04, A10AB05, A10AB06, A10AC01, A10AC04, A10AD01, A10AD04, A10AD05, A10AD06, A10AE01, A10AE04, A10AE05, A10AE06, A10AE54, A10AE56, A10BA02, A10BA03, A10BB, A10BB01, A10BB02, A10BB03, A10BB09, A10BB12, A10BB31, A10BD, A10BD05, A10BD06, A10BD08, A10BD09, A10BD13, A10BD19, A10BF01, A10BF02, A10BF03, A10BG03, A10BH, A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BH08, A10BJ01, A10BJ02, A10BJ03, A10BJ05, A10BJ06, A10BK, A10BK01, A10BK02, A10BK03, A10BK05, A10BK07, A10BX, A10BX02, A10BX03, A10BX08, A10XA
Methotrexate	L04AX03
Mycophenolate	L04AA06
Ribavirin	J05AP01
SSRIs	N06AB05, N06AB06, N06AB08, N06AB10
Statins	C10AA01, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08
Warfarin	B01AA03

WHO ACT: World Health Organization Anatomical Therapeutic Chemical

To quantitatively assess the representativeness of the mother–infant linked cohort relative to the target population of all mothers and liveborn infants in Japan, we leveraged publicly available data regarding the prevalence of maternal and infant health conditions from the GHDx and Japanese Vital Statistics. The GHDx is a public data catalog created and maintained by the Institute for Health Metrics and Evaluation, which provides global data on demographics and health conditions. As part of this data catalog, results from the GBD global descriptive epidemiology study are available from 1990 to 2019.[67] The GBD study captures information on nearly 370 diseases and injuries in 204 countries and territories, with stratification available on age and sex. The GHDx GBD visualization tool (https://vizhub.healthdata.org/gbd-results/) was used to examine the prevalence of selected medical conditions among females age 10–54 (the closest age group to our cohort inclusion criteria) and the prevalence of infant (age <1 year) major congenital malformations in Japan from 2005–2019, to most closely match our data availability. We selected maternal medical conditions based on those likely to be important treatment indications or confounders in future analyses (**Table 2**). The total prevalent number of

cases and the total population size for each condition were used to generate annual prevalence, and the average across all years was calculated as a summary measure for each condition.

Demographic characteristics for all annual births in Japan are available from the Japanese Vital Statistics natality data (https://www.e-stat.go.jp). This source offers a complete capture of births in Japan, as reporting is required by law. Information elicited on the live birth form includes maternal age, infant sex, infant weight, weeks of gestation, place of delivery (e.g., hospital or home), and geographic area of residence.[68] We obtained the average maternal age, the distribution of infant sex, and gestational age category (preterm versus term) from 2010 to 2019 (maximum data years available during our study period; note gestational age group was not available for 2011 to 2013).[68]

Although we also would have liked to explore how well the mother–infant linked population in the JMDC represents the target population of all mothers and liveborn infants in Japan in terms of prescription medication utilization and healthcare utilization, the level of detail desired regarding these characteristics is not well-reported in the literature nor any publicly available Japanese data source. It is worth noting that we did explore the open data provided by the National Database of Health Insurance Claims and Specific Health Checkups of Japan. This source does annually report aggregated information regarding the number of monthly prescribed pharmaceutical products, according to product name and patient sex and age group. However, due to the ecological nature of this database, we were unable to determine the proportion of unique females of childbearing age receiving medications in each drug class.

Finally, to quantitatively assess the representativeness of the mother–infant linked cohort relative to all mothers and liveborn infants in the JMDC database, we examined characteristics among the unlinked population. Understanding how those successfully matched may differ from unmatched and excluded infants and mothers is important for informing the generalizability (i.e., whether and how results would need to be reweighted to inform treatment decisions for all

mothers and liveborn infants in Japan) of future pregnancy safety and effectiveness studies conducted in such linked databases, which has important implications regarding to whom the results derived from this source of real-world data could be applied. Specifically, for females with evidence of a live birth delivery but without a successful linkage to their infant (i.e., those identified in Linkage Method A step 2, minus those linked to an infant in step 2iv), medical conditions, prescription medications, and enrollment characteristics were assessed relative to the delivery date. For infants without a successful linkage to their mother (i.e., all infants in the JMDC claims database minus those linked to a mother in Linkage Method B step 1), major congenital malformations and enrollment characteristics were assessed relative to the estimated date of birth (set as 15th day of birth month).

Results

There were 5,795,818 females ages 12–55 years and 717,034 infants identified during the study period. According to Linkage Method A, 643,483 unique pregnancy episodes were identified according to the presence of active pregnancy codes, among which 257,885 (40%) successfully linked with an infant. After removal of 19,307 pairs (8%) due to invalid relationships or duplicate infants, a total of 238,578 valid pairs remained. Additionally, Linkage Method A identified 320,051 unique pregnancy episodes according to the presence of delivery codes, 178,751 (56%) of which successfully linked with an infant. After removal of 12,766 pairs (7%) due to invalid relationships or duplicate infants, a total of 165,985 valid pairs remained. Comparison of the valid pairs from the active pregnancy and delivery code groups revealed a total of 276,027 unique pairs identified via Linkage Method A.

According to Linkage Method B, 446,441 total unique pairs were identified via family identification codes. Among these pairs, 300,706 (67%) possessed active pregnancy and/or delivery codes, with the remaining 145,705 pairs (33%) having neither active pregnancy nor

delivery codes. After removal of 61,116 (14%) due to invalid relationships or duplicate infants, a total of 385,295 valid pairs remained. These results are discussed in more detail in the context of the Duke-Margolis framework in the following sections.

1. Data Relevancy

The relevancy of a given real-world database relates to the capacity of the database to answer the regulatory research question, in terms of the availability of critical data fields and a sufficiently sized, representative population.

1.1. Availability of Key Data Elements

To assess data relevancy, we first considered whether critical data fields required to address the research question were available: the exposure (maternal medication exposure), the outcome (infant major congenital malformations), potential covariates of interest, and data fields permitting patient-level mother–infant linkage.

1.1.1. Exposure (Maternal Medication Exposure)

The Japanese National Health Insurance System covers most medical services, including drugs (except for over-the-counter drugs). The absence of information regarding over-the-counter medications in the JMDC claims database is not of concern given that the regulatory context for the present analysis states a particular interest in post-authorization examination of marketed medications. The JMDC claims database contains records of all prescribed medications, with detailed information available regarding dates of dispensing, the prescribed daily dose, and the number of days administered.[45] These prescription claims are expected to offer a complete representation of all medications prescribed to mothers before and during pregnancy (i.e., high exposure sensitivity), as needed to define the exposure of interest. Prescription information obtained from claims data offers advantages over survey-based information collected as a part of pregnancy exposure registries, which is often subject to recall bias.[46] However, all claims

databases have inherent limitations because the claims are collected for the purpose of payment and not research. Presence of a claim for a filled prescription does not indicate that the medication was consumed, which could contribute to low exposure positive predictive value. Importantly, exposure definition with respect to the etiologically relevant window requires knowledge of prescription consumption timing relative to gestational age (**Figure 1)** which is discussed in more detail as part of the data quality considerations.

1.1.2. Outcome (Infant Major Congenital Malformations)

The JMDC claims database contains diagnoses (classified according to ICD-10) and medical procedures from the inpatient and outpatient settings, all with dates available.[45] All infants in Japan are enrolled in the National Health Insurance System within one month of birth and the JMDC claims database captures all infant medical visits. Capture of infants diagnosed with major congenital malformations, as needed to define the outcome of interest, is therefore expected to be complete. As previously stated, all claims databases have inherent limitations. Presence of a diagnosis code on a medical claim is not necessarily indicative of the presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual diagnosis of a disease or condition. Similarly, the absence of a diagnosis code on a medical claim may not necessarily indicate the absence of a disease or condition, for example due to a missed diagnosis, an error in reporting, or the possibility that a condition present at birth is not clinically manifest until a later age. For the serious diagnoses we plan to consider, the presence of an associated claim will be assumed to validly indicate that the disorder was present and the absence of a claim will indicate the opposite. Validation of a JMDC claims-based algorithm to identify any infant major congenital malformations against gold standard medical records in Japan found the positive predictive value to be 91.5% (95% CI 85.6%–95.5%); negative predictive value was not reported.[69]

1.1.3. Covariates

The JMDC claims database contains diagnoses (classified according to ICD-10) and medical procedures from the inpatient and outpatient settings, all with dates available.[45] We therefore expect to be able to measure demographic characteristics and comorbidities, concomitant medications, and healthcare utilization characteristics as required to address confounding of the exposure-outcome association of interest. As previously mentioned, there are general limitations of using claims databases for research purposes (e.g., whether the presence versus absence of a diagnosis code corresponds to the true disease state). However, for the serious diagnoses and related concomitant medication usage likely to be considered as confounders of the relationship between maternal medication use and infant major congenital malformations, the presence of an associated claim will be interpreted as indicating that the procedure was conducted, the disease was present, or the drug was consumed. The absence of a claim will indicate the opposite. Missing data will be a concern mainly when lifestyle (e.g., alcohol use, smoking, physical activity) and biometrics (e.g., body mass index, blood pressure, cholesterol) are important covariates for a given analysis, because these items are not well captured in claims. Additionally, certain pregnancy-related characteristics that may be important confounders of the association between *in utero* medication exposure and infant major congenital malformations, such as reproductive history, are also not well-captured in claims databases.[46]

1.1.4. Patient-Level Linking (Linkage of Maternal and Infant Records)

Healthcare claims, which are collected for billing purposes, do not inherently indicate correspondence between mothers and their infants and therefore this information must be reconstructed by researchers.[36-45] Linkage of mothers and infants in the JMDC claims database is possible if the two parties share a health insurer. Health insurance benefits are provided not only to the insured individual, but also to their dependent family members. A unique, shared

family identification variable is assigned to the insured individual and their enrolled dependents, enabling linkage of maternal and infant records based on this value. Further detail regarding the accuracy of mother–infant pairs formed using the family identification variable is discussed below as part of the data quality considerations.

1.2. Representativeness

The next data relevancy consideration relates to the ability of the persons in the database to accurately reflect the population of interest. Here, we assessed whether the persons in the linked mother–infant JMDC population were expected to be representative of the population of interest (i.e., pregnant people in Japan and their liveborn infants). Although mother–infant linked populations have previously been created in varied claims databases (e.g., the Medicaid Analytic eXtract,[36] the IBM Watson Health MarketScan Databases,[41] the Mini-Sentinel Distributed Database[39]), the representativeness of mothers and infants included in the cohort relative to the target population has not been assessed. Descriptive analysis of a mother–infant linkage in the Sentinel Distributed Database revealed that linked versus unlinked pairs had a higher average maternal age and were less likely to be preterm deliveries, but were otherwise similar according to most pre-pregnancy maternal comorbidities and features of healthcare utilization.[70] It is not clear whether this observation would hold true for mother–infant linkages in other databases.

We compared the distributions of the characteristics of the mother–infant linked cohort with the general Japanese population and with the unlinked mothers and infants in the JMDC claims database (**Table 4**).

Table 4. Prevalence of maternal medical conditions, medication use, and infant major congenital malformations in the Japan Medical Data Center (JMDC) claims database linked and unlinked populations, compared to the general Japan population

	General Japan Population	JMDC Linked, All Valid Pairs	JMDC Linked, Valid Pairs with Codes	JMDC Unlinked[1]
Female Characteristics[2]		**N = 287,444**	**N = 207,681**	**N = 119,676**
Demographic Characteristics[3]				
Age, years (mean)	31.7	32.3 (SD 5.0)	32.6 (SD 5.0)	32.6 (SD 5.0)
Medical Conditions[4]				
Alcohol use disorders	0.5% (0.4%, 0.7%)	0.1%	0.1%	0.2%
Anxiety disorders	3.5% (2.9%, 4.1%)	2.9%	3.5%	4.7%
Asthma	4.1% (3.1%, 5.2%)	11.4%	13.5%	19.8%
Breast cancer	0.6% (0.6%, 0.7%)	0.1%	0.1%	0.2%
Cervical cancer	0.1% (0.1%, 0.1%)	0.1%	0.1%	0.2%
Diabetes mellitus	1.9% (1.7%, 2.2%)	1.0%	1.3%	1.3%
Idiopathic epilepsy	0.2% (0.1%, 0.3%)	0.6%	0.7%	0.6%
Major depressive disorder	2.4% (2.1%, 2.8%)	2.2%	2.6%	3.5%
Maternal hypertensive disorders	0.1% (0.0%, 0.1%)	5.9%	8.0%	8.9%
Migraine	20.2% (17.4%, 23.4%)	3.6%	4.3%	5.7%
Substance use disorders	1.5% (1.3%, 1.7%)	0.2%	0.2%	0.5%
Medication Use				
ACE-Is	Not reported	0.0%	0.0%	0.0%
Anti-diabetics	Not reported	1.2%	1.6%	1.2%
Anticonvulsants	Not reported	0.5%	0.7%	0.7%
Methotrexate	Not reported	0.0%	0.0%	0.0%
Mycophenolate	Not reported	0.0%	0.0%	0.0%
SSRIs	Not reported	0.5%	0.7%	0.6%
Statins	Not reported	0.1%	0.1%	0.1%
Warfarin	Not reported	0.0%	0.0%	0.0%
Infant Characteristics[5]		**N = 385,295**	**N = 275,352**	**N = 410,179**
Demographic Characteristics[3]				
Preterm versus term				
Preterm (<37 weeks)	5.6%	3.6%	4.1%	3.3%
Term	94.3%	96.4%	95.9%	96.7%
Sex				
Male	51.3%	51.2%	51.1%	51.3%
Female	48.7%	48.8%	48.9%	48.7%
Major Congenital Malformations[4]				
Any major congenital malformation[6]	5.3% (4.6%, 6.2%)	10.8%	11.1%	11.2%
Congenital heart anomalies	1.2% (1.0%, 1.6%)	2.8%	3.0%	2.7%
Congenital musculoskeletal/limb anomalies	2.1% (1.4%, 2.8%)	1.7%	1.7%	1.8%
Digestive congenital anomalies	0.5% (0.4%, 0.6%)	0.5%	0.5%	0.5%
Down syndrome	0.1% (0.1%, 0.1%)	0.2%	0.2%	0.1%
Klinefelter syndrome	0.0% (0.0%, 0.0%)	0.0%	0.0%	0.0%
Neural tube defects	0.0% (0.0%, 0.0%)	0.2%	0.2%	0.2%
Orofacial clefts	0.2% (0.1%, 0.3%)	0.2%	0.2%	0.2%
Other chromosomal abnormalities	0.7% (0.6%, 0.8%)	0.1%	0.2%	0.1%
Other congenital birth defects	0.1% (0.0%, 0.1%)	6.2%	6.3%	6.7%
Turner syndrome	0.1% (0.0%, 0.1%)	0.0%	0.0%	0.0%
Urogenital congenital anomalies	0.9% (0.7%, 1.2%)	0.3%	0.4%	0.4%

[1]Unlinked population represents two separate cohorts: (1) females with delivery codes without a paired infant and (2) infants without a paired mother.
[2]Female characteristics assessed among total number of unique females. If a female had more than one delivery during the study period, a single delivery was randomly selected.
[3]General Japan population data obtained from Japanese Vital Statistics.
[4]General Japan population data obtained from the Global Burden of Disease Study.
[5]Infant characteristics assessed among total number of unique infants (equivalent to total number of unique mother–infant pairs).
[6]Does not equate to a simple sum of the individual major congenital malformation categories due to some infants possessing >1 major congenital malformation.
ACE-Is: Angiotensin-converting enzyme inhibitors. SSRIs: Selective serotonin reuptake inhibitors.

There were no differences between the JMDC population and the general Japan population in terms of maternal age or infant sex distribution. In the JMDC linked population, preterm birth was observed in 3.6% of mother–infant pairs, compared to 5.6% in the general Japan population. Restricting the JMDC population to those with pregnancy or delivery codes (which did include preterm birth codes) increased the preterm birth prevalence to 4.1%. Comparison of the JMDC linked population to the population of unlinked mothers and infants in the database did not reveal any differences in the distributions of maternal age or preterm birth. Although this differs from a previously published descriptive analysis of a mother–infant linkage in the Sentinel Distributed Database, which observed that linked versus unlinked pairs had a higher average maternal age and were less likely to be preterm, this discrepancy may be due to differences in the healthcare systems of the US versus Japan.[70]

The population of valid pairs, compared to the general Japanese population of same-aged females in Japan, had a similar prevalence of anxiety disorders (2.9% versus 3.5%), diabetes mellitus (1.0% versus 1.9%), major depressive disorder (2.1% versus 2.4%), and cervical cancer (0.1% versus 0.1%). The prevalence of alcohol and substance use disorders were lower in the JMDC linked population compared with the general population, but these conditions are generally under-captured in claims databases.[71, 72] Additionally, the prevalence of migraine was lower among the JMDC linked population compared with the general Japan population (3.6% versus 20.2%). Similar observations of lower migraine prevalence than the general Japanese population have been previously made in populations of JMDC patients, potentially due to the claims database representing migraine patients seeking medical care (i.e., the severe migraine population).[73-75] Maternal hypertensive disorders were more common in the JMDC linked population (5.9%) as expected given that the general Japan prevalence (0.1%) was not restricted to pregnant people. Asthma was also more common in the JMDC linked population compared with the general Japan population (11.4% versus 4.1%), which may be attributable to

our assessment of medical conditions on all available patient history detecting a more prevalent lifetime history of asthma, rather than current asthma.[76, 77] Notably, the prevalence of chronic conditions (anxiety disorders, asthma, major depressive disorder, migraine), as well as maternal hypertensive disorders, were higher among the JMDC linked population with pregnancy or delivery codes, as compared to the total linked population, perhaps due to this population having a greater likelihood of healthcare utilization. Restriction of the linked population to those with pregnancy or delivery codes, however, did not result in any major changes to the medication use prevalence.

Total infant major congenital malformations were more prevalent in the JMDC linked population (10.8%) compared to the general Japan population (5.3%). This heightened prevalence in the JMDC linked population, compared to the general population, appeared to be driven by a higher prevalence of congenital birth defects in the “other” category (6.2% versus 0.1%); the prevalence of most of the alternative congenital malformation subtypes, however, were the same or similar between the two populations (e.g., congenital musculoskeletal and limb anomalies, digestive congenital anomalies, Down syndrome, orofacial clefts, Klinefelter syndrome, Turner syndrome). Other chromosomal abnormalities (0.1% versus 0.7%) and urogenital congenital anomalies (0.3% versus 0.9%) occurred less often in the JMDC population compared to the general Japan population. There were two ICD-10 codes used in the definition for other chromosomal abnormalities in the general Japan population that were unavailable in the JMDC claims database (Q95 and Q97.9), which may have contributed to the lower prevalence observed in the JMDC. Notably, removing other congenital birth defects from the total major congenital malformation prevalence resulted in a more similar estimate in the JMDC linked population (5.5%) compared with the general Japan population. We suspect that this “other” congenital birth defects category may be acting as a catch-all category that encompasses many congenital anomalies, both major and minor, therefore resulting in an

apparently higher prevalence in the JMDC claims database. Comparison of the prevalence of each major congenital malformation subtype to the prevalence reported in population-based literature from Japan supports the comparability of the JMDC linked pairs to the general Japan population in terms of the prevalence of specific major congenital malformation subtypes (**Table 5**). It is unlikely that future pregnancy safety studies would specify the primary outcome of interest as "other" congenital birth defects, but rather would likely be using the alternative specific subtypes, and therefore we do not consider the observed heightened prevalence of "other" congenital birth defects to be a major flaw of the JMDC claims database.

Table 5. Prevalence of infant major congenital malformations in the Japan Medical Data Center (JMDC) claims database linked and unlinked populations, compared to Japanese population-based literature estimates

Major Congenital Malformations[1]	Japan Literature Mean (Min, Max)	JMDC Linked, All Valid Pairs	JMDC Linked, Valid Pairs with Codes	JMDC Unlinked
Congenital heart anomalies[78-83]	2.6% (0.3%, 5.0%)	2.8%	3.0%	2.7%
Congenital musculoskeletal/limb anomalies[80, 82, 83]	0.7% (0.4%, 1.3%)	1.7%	1.7%	1.8%
Digestive congenital anomalies[80-85]	0.4% (0.1%, 1.3%)	0.5%	0.5%	0.5%
Down syndrome[80-84, 86]	0.3% (0.1%, 0.9%)	0.2%	0.2%	0.1%
Neural tube defects[80, 82-84, 87]	0.1% (0.0%, 0.4%)	0.2%	0.2%	0.2%
Orofacial clefts[80-84]	0.4% (0.2%, 1.0%)	0.2%	0.2%	0.2%
Other chromosomal abnormalities[80-84]	0.3% (0.0%, 0.9%)	0.1%	0.2%	0.1%
Turner syndrome[80, 88]	0.1% (0.0%, 0.2%)	0.0%	0.0%	0.0%
Urogenital congenital anomalies[80-85]	0.6% (0.1%, 1.3%)	0.3%	0.4%	0.4%
Total[2]	**5.4% (1.2%, 12.2%)**	**6.0%**	**6.4%**	**6.0%**

[1]Literature estimates not available for Klinefelter syndrome and other congenital birth defects, which have been removed here and are not included in the totals.
[2]Sum of individual categories computed as a descriptive summary to allow for comparison across sources. Does not equate to a total population prevalence due to some infants possessing >1 major congenital malformation.

Restricting to mother–infant pairs with pregnancy or delivery codes did not result in substantial changes in the congenital birth defect prevalence (from 10.8% to 11.1%). The similar congenital birth defect prevalence between these two groups suggests that the presence of pregnancy and delivery codes, as needed for the definition of the gestational period and thereby the critical exposure window, may not vary according to occurrence of congenital birth defects (i.e., non-differential with respect to outcome).

The population of unlinked mothers, compared to the population of all valid pairs, was more likely to have most of the medical conditions examined. Most notably, the unlinked versus linked had a higher prevalence of anxiety disorders (4.7% versus 2.9%), asthma (19.8% versus 11.4%), and maternal hypertensive disorders (8.9% versus 5.9%). The prevalence of medication use was similar for the unlinked and linked populations across all medication classes examined. The population of unlinked infants, compared to the population of all valid pairs, had a slightly higher prevalence of major congenital malformations (11.2% versus 10.8%), which was mainly driven by a higher prevalence of other congenital birth defects (6.7% versus 6.2%).

1.3. Sufficient Subjects

Another component of data relevancy is the evaluation of whether there are sufficient persons in the data source that would allow for valid and precise estimation of the expected treatment effect. Here, we evaluated whether the linked population of mothers and infants was expected to be sufficiently large, with sufficient outcome events among the infants. Japan's pharmaceutical market is one of the largest in the world, with further growth expected in the next decade, and the JMDC is Japan's largest claims database, making it a strong choice of real-world data to efficiently evaluate the safety and effectiveness of drug products in the Japanese population.[64, 89] The JMDC is compiled from over 1,400 private companies that belong to the Health Insurance Association, one of the five payer organizations of the Japanese National Health Insurance System. All citizens of Japan are covered by the National Health Insurance System, provided either through their employer or through the government. As most included companies in the Health Insurance Association (the source of the JMDC claims database) are employer-based, the 29 million members are typically salaried workers and their families, all of whom are ages 74 years or younger. The most recent JMDC data release at the time of this analysis contained approximately 14 million individuals insured between January 2005 and March 2022.

According to comparison of the count of infants enrolled in a JMDC-covered health plan in their birth month (e.g., 86,897 members born in 2021) with annual live birth vital statistics data from the Japanese government (e.g., 811,622 live births in 2021[68]), we estimated that the JMDC claims database captured around 4% of all annual live births in Japan from 2005 to 2022 (annual range 0–11%) (**Table 6**). Notably, the percentage of annual live births in Japan that were captured in the JMDC database increased over the study period, such that in 2018 to 2021 the JMDC captured 9–11% of live births in Japan.

Table 6. Summary of annual births in the Japan Medical Data Center (JMDC) claims database among linked mother–infant pairs, compared to the general Japan population

Year	Total Annual Births in Japan	Total Number of JMDC Covered at Birth	Total Valid Pairs, Linkage Method A	Total Valid Pairs, Linkage Method B	Total Valid Pairs with Codes, Linkage Method B
2005	1,062,530	4,167	1,002	1,714	981
2006	1,092,674	4,585	1,267	1,893	1,253
2007	1,089,818	4,765	1,410	2,015	1,398
2008	1,091,156	6,062	1,960	2,901	1,934
2009	1,070,036	8,903	3,380	4,857	3,336
2010	1,071,305	14,614	6,068	9,170	6,000
2011	1,050,807	18,518	8,212	11,913	8,181
2012	1,037,232	24,735	10,819	15,791	10,770
2013	1,029,817	34,879	15,344	22,465	15,301
2014	1,003,609	38,265	16,790	23,784	16,767
2015	1,005,721	52,451	21,433	30,824	21,408
2016	977,242	64,121	26,168	37,098	26,154
2017	946,146	78,747	31,502	44,359	31,500
2018	918,400	86,014	33,335	46,191	33,327
2019	865,239	88,590	32,913	45,301	32,842
2020	840,835	89,644	31,797	42,741	31,724
2021	811,622	86,897	29,017	37,619	28,889
2022	799,728	11,077	3,610	4,659	3,587
Total	***17,763,917***	***717,034***	***276,027***	***385,295***	***275,352***

Of the total infants covered at birth in the JMDC database, we found that 54% (annual range 41–64%) were validly linked to a mother according to Linkage Method B (**Table 6**). When we required the presence of pregnancy and/or delivery codes, the valid linkage rate for infants

covered at birth decreased to 38% (annual range 24–44%).

Of the linked, valid pairs from Linkage Method B, the expected number of outcome events is presented in **Table 7**. Among all valid pairs, about 41,000 infant major congenital malformations were observed within one year of birth. The most common outcomes were congenital heart anomalies (N = 10,934) and other congenital birth defects (N = 23,954). All additional major congenital malformations subtypes had greater than 500 events, except for the rare events Klinefelter syndrome (N = 9) and Turner syndrome (N = 13), both of which are often diagnosed later in life. After excluding other congenital birth defects from the total prevalence (due to concerns previously described in 1.2. Representativeness), a total of 21,176 major congenital malformations occurred among all valid pairs.

Table 7. Expected events of infant major congenital malformations among linked mother–infant pairs in the Japan Medical Data Center (JMDC) claims database

Outcome	All Valid Pairs (N = 385,295) N	Valid Pairs with Codes (N = 275,352) N
Congenital heart anomalies	10,934	8,333
Congenital musculoskeletal and limb anomalies	6,462	4,794
Digestive congenital anomalies	1,799	1,373
Down syndrome	628	456
Klinefelter syndrome	9	8
Neural tube defects	747	567
Orofacial clefts	706	528
Other chromosomal abnormalities	556	408
Other congenital birth defects	23,954	17,404
Turner syndrome	13	12
Urogenital congenital anomalies	1,291	966
Any major congenital malformation[1]	***41,438***	***30,571***

[1]Does not equate to a simple sum of the individual major congenital malformation categories due to some infants possessing >1 major congenital malformation.

Of the linked, valid pairs from Linkage Method B, the expected numbers of mothers exposed to various prescription medications in the year before delivery are presented in **Table 8**. There were 3,395 mothers exposed to anti-diabetics during pregnancy and about 1,500 each exposed to anticonvulsants and SSRIs; other medication exposures occurred more rarely.

Table 8. Expected distribution of prescription medication exposure among linked mother–infant pairs in the Japan Medical Data Center (JMDC) claims database

Prescription Medication	All Valid Pairs (N = 385,295) N	Valid Pairs with Codes (N = 275,352) N
ACE-Is	35	35
Anti-diabetics	3,395	3,366
Anticonvulsants	1,567	1,429
Methotrexate	15	13
Mycophenolate	5	4
SSRIs	1,511	1,399
Statins	155	141
Warfarin	46	44

ACE-Is: Angiotensin-converting enzyme inhibitors. SSRIs: Selective serotonin reuptake inhibitors.

Rothman and Greenland have derived a method to plan the size of an epidemiologic study based on precision (i.e., desired width of the confidence interval for the effect estimates), rather than power as has typically been done, to divert focus from statistical significance testing.[90] Given our knowledge of the sample size we would expect in future studies using the cohort of valid pairs from Linkage Method B (N = 385,295), we may use their equation to achieve the expected width of the confidence interval (ratio of upper to lower limit) and make an assessment of whether the value is sufficient. Given the expected count of all infant major congenital malformations (N = 41,438) and the expected counts of mothers exposed to anti-diabetics (N = 3,395), under the null (equal outcome event rates among those exposed and those unexposed), we would expect to obtain 95% confidence intervals with a ratio of upper/lower limit of 1.2 for the association between anti-diabetics and all major congenital malformations.[90] If we wish to examine the association between a less common medication class (e.g., SSRIs, N = 1,511) and all major congenital malformations, this ratio increases to 1.3. If we were to examine specific major congenital malformations separately, the width of the expected confidence intervals would further increase (e.g., 1.8 for the association between SSRIs and congenital heart anomalies). The associations between anti-diabetics, anticonvulsants, or SSRIs with congenital heart anomalies, congenital musculoskeletal and limb anomalies, other congenital birth defects, or

total congenital anomalies (both with and without “other” congenital birth defects included) were the only exposure–outcome combinations with expected precision less than or equal to 2.2; all other medication exposures and congenital malformation outcomes resulted in insufficient precision estimates. These results suggest that the JMDC mother–infant linked population may have sufficient subjects to study some, but not all, *in utero* medication exposures and infant congenital malformations.

1.4. Longitudinality

The final component of data relevancy is the evaluation of whether there is sufficient follow-up time in the data source to estimate the treatment effect. We evaluated whether the mothers were under follow-up for the entire pregnancy (i.e., continuous enrollment) and the infants were under follow-up for a sufficient timeframe to observe outcomes. Mother–infant linkages in claims databases often require continuous health plan enrollment of mothers during pregnancy to ensure accurate and complete capture of prescription dispensing. It is also important to understand the proportion of infants that remain enrolled during the follow-up period to understand the proportion of censoring due to loss to follow-up that would occur in future studies of *in utero* medication exposures and infant major congenital malformations. We therefore assessed the percentage of mothers who had continuous enrollment during pregnancy, the distribution of pre-pregnancy continuous enrollment, and the expected percentage of infants who have at least a year of follow-up time. This evaluation of infant follow-up allows for malformations to be detected throughout the first year of life, which is a generous follow-up period given that most (94%) congenital malformations are recorded in the first 90 days of life.[91]

Among the population of all valid pairs, 57% of mothers were continuously enrolled in their health plan throughout the pregnancy period, with 46% continuously enrolled both during pregnancy and in the 180 days before pregnancy (**Table 9**). At least one year of infant follow-up

was available for 86% of valid pairs. We observed that 49% of valid pairs had both maternal continuous enrollment during pregnancy and at least one year of infant follow-up. Restriction of valid pairs to those with pregnancy or delivery codes did not change the distributions of pre-pregnancy continuous enrollment or infant follow-up but did result in an increase of the proportion with continuous enrollment during pregnancy (68%), perhaps due to a greater likelihood for these females to be engaging with the healthcare system during pregnancy. These results suggest that future pregnancy safety studies in the JMDC claims database that require continuous enrollment during pregnancy may suffer from limited sample sizes and a potentially high proportion of censoring during the follow-up period. Given that all individuals in Japan are covered by the National Health Insurance, and that pregnancy-related care is subsidized under a government maternity voucher program, we do not suspect that lack of continuous enrollment in the JMDC claims database is reflective of gaps in the continuity of care received during pregnancy, but rather may be a result of changes in the contracts between the JMDC data vendor and the private companies that provide claims to the database.

Table 9. Maternal and infant enrollment characteristics among linked mother–infant pairs in the Japan Medical Data Center (JMDC) claims database

	All Valid Pairs (N = 385,295) N (%)	**Valid Pairs with Codes (N = 275,352) N (%)**
Maternal continuous enrollment during pregnancy	218,560 (56.7%)	186,676 (67.8%)
Length of pre-pregnancy continuous enrollment		
Not enrolled at pregnancy onset[1]	166,735 (43.3%)	88,676 (32.2%)
≤30 days	7,227 (1.9%)	6,251 (2.3%)
31–90 days	13,556 (3.5%)	11,702 (4.2%)
91–180 days	18,913 (4.9%)	16,209 (5.9%)
>180 days	178,864 (46.4%)	152,514 (55.4%)
Length of infant follow-up		
≤30 days	0 (0.0%)	0 (0.0%)
31–90 days	9,207 (2.4%)	7,154 (2.6%)
91–180 days	14,649 (3.8%)	11,251 (4.1%)
181–365 days	28,798 (7.5%)	21,936 (8.0%)
≥366 days	332,641 (86.3%)	235,011 (85.4%)
Both maternal continuous enrollment during pregnancy and at least 365 days of infant follow-up	186,826 (48.5%)	158,838 (57.7%)

[1]Only females continuously enrolled during pregnancy were enrolled at the onset of pregnancy and therefore were eligible for assessment of pre-pregnancy continuous enrollment.

2. Data Quality

The quality of a real-world database relates to ability of the data source to accurately, reliably, and transparently answer the regulatory question of interest. We considered two separate processes involved in the creation of a mother–infant linked population in the JMDC claims database as needed for target trial emulation that could impact data quality: (A) the formation of the mother–infant matches and (B) the estimation of the gestational period.

2.A. Mother–Infant Matches

As previously described, healthcare claims do not inherently indicate correspondence between mothers and their infants and therefore this information must be reconstructed by researchers to emulate a pregnancy target trial.[35-45] Our consideration of whether a linked cohort of mothers and infants in the JMDC claims database is fit for regulatory purposes therefore involved assessment of the quality of these matches in terms of the completeness and accuracy as well as the transparency of the linkage process.

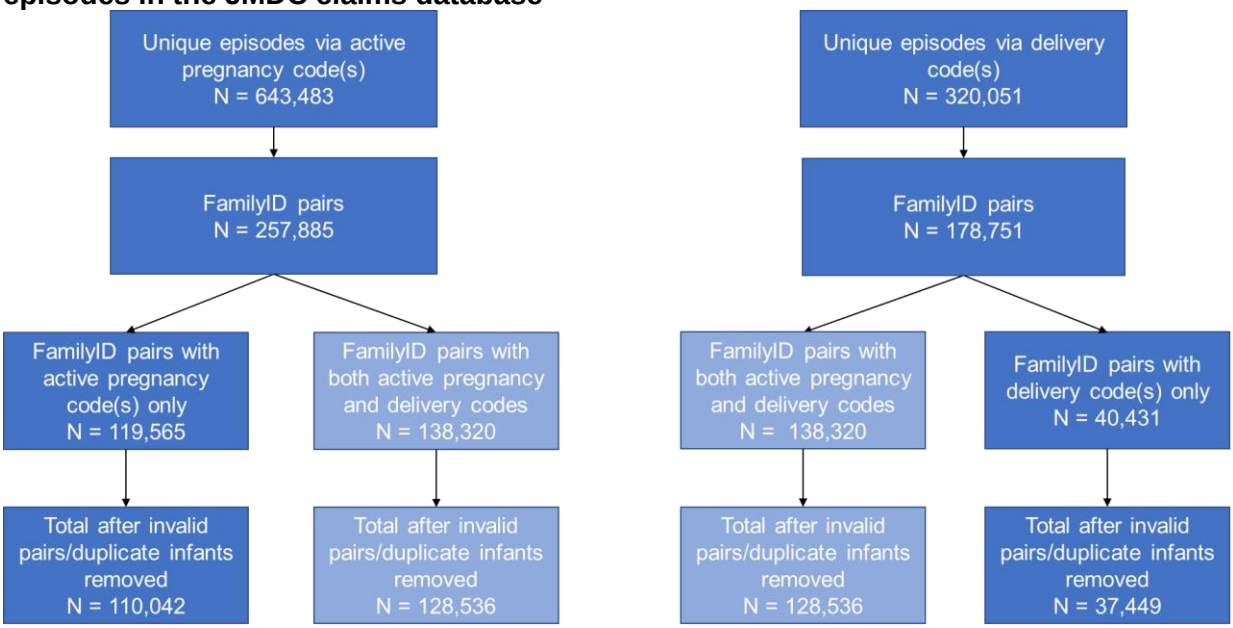
2.A.1. Completeness

The completeness of the data relates to the extent and potential mechanisms of missingness. In this example, we considered whether the mother–infant linkage process was expected to identify the complete set of mothers and infants in the JMDC. Our method is expected to capture all mothers and infants who were enrolled in a shared health insurance plan. All infants in Japan are enrolled in the National Health Insurance System within one month of birth, so even deliveries that may occur outside of the healthcare setting (only 0.2% of deliveries, according to Japan Vital Statistics[68]) would still be captured in the JMDC and linked to a mother given a shared insurance plan.

It is important to consider the pregnancies that are identifiable in the JMDC that do not successfully link to an infant to understand the completeness of the linked pairs. We assessed

the number of mother–infant linkages relative to the estimated number of unique pregnancy episodes identifiable in the JMDC claims database to evaluate the proportion of pregnancies that did not link to an infant (**Figure 8**). The linkage rate was 56% for pregnancy episodes identified via live birth delivery codes, yet was only 40% for pregnancy episodes identified via active pregnancy codes (nearly half of which were found to be missing live birth delivery codes). These linkage rates are expected given the likelihood of liveborn infants to be covered under their mother's insurance plan, as compared to the insurance plan of the other parent. The pregnancy episodes that lacked live birth delivery codes likely disproportionately included pregnancies that ended in non-live birth outcomes (e.g., spontaneous abortion, stillbirth), thereby resulting in the apparently lower linkage rate.

Figure 8. Assessment of mother–infant linkages relative to total unique pregnancy episodes in the JMDC claims database



FamilyID: Family identification code

We also examined the number of mother–infant linkages relative to the number of annual infant births in the JMDC to evaluate the proportion of infants that do not link to a mother (see **Table 6**). Of the annual live births captured in the JMDC (defined as an infant enrolled in the JMDC in the same month as the birth month), we found that 54% (annual linkage rate range 41–64%)

were able to be linked to a mother. This aligns with expectations of the proportion of infants who would be covered under their mother's, versus other parent's, health insurance plan.

2.A.2. Accuracy

The next data quality element is related to whether the data are expected to be accurate. This assessment involved considering the validity, logical plausibility, and consistency of the mother–infant linked pairs.

2.A.2.1. Validity

One element of data accuracy is validity, which is a measure of concordance between a data field and a definitive measure. To assess validity of the linked mothers and infants, we considered whether the linkage process was expected to match up true mother–infant pairs (i.e., whether the family identification variable was a valid indicator of family relation). Unfortunately, the JMDC does not provide documentation related to the validity of the family identification variable, which limits our capability for comprehensive assessment. When an individual is enrolled as the insurance plan holder in a JMDC covered plan, they are assigned a unique identification variable. That same unique identifier is also entered as their family identification code, even if they do not have any dependents. When dependents are added to the plan, this shared family indication code is assigned to allow connection between the records of the dependent and the insurance plan holder for billing purposes. Given that the family identification codes are generated and used for billing, rather than research purposes, it is expected that they should correctly indicate correspondence between insured individuals and their dependents.

2.A.2.2. Conformance

Another element of data accuracy is conformance, which describes whether the data are congruent with standardized types, sizes, and formats. As stated above, there is unfortunately a

scarcity of detailed information available from the JMDC regarding the assignment and entry of family identification codes into the database. The family identification codes, however, are always assigned, regardless of the presence or number of dependents corresponding to an insured individual, and are never missing. This variable therefore presumably conforms to database rules. Furthermore, given that family identification codes are created and used for billing purposes, creation and maintenance of the claims database itself does not disrupt this information and it is thus expected to remain congruent with the standard.

2.A.2.3. Logical Plausibility

Data accuracy also implies that the recorded values are logically believable. In other words, whether the “mothers” and “infants” who were linked were plausible mother–infant pairs. As previously mentioned, health insurance benefits are provided not only to the insured individual, but also to their dependent family members. **Figure 9** displays the results of the cross-tabulation of the value of the relationship to insurance holder for all pairs linked based on matching family identification codes (Linkage Method B), assuming incestuous relationships to be improbable.

Of 446,411 total family matches between potential mothers and their infants, inspection of the combination of values for the relationship of both to the insurance holder revealed that 400,730 (90%) were confident biological mother–infant pairs (i.e., the infant is listed as being the child of either the insurance holder themselves or the spouse of the insurance holder). For 0.5% (N = 2,225) of the matches, a biological mother–infant relationship was possible but not definite (e.g., the “mother” is the sibling of the insurance holder and the “infant” is the nephew/niece of the insurance holder). Although only a small percentage, 2.5% (N = 11,340), of matches warranted exclusion due to being assumed implausible mother–infant pairs (e.g., the “mother” and the “infant” are both children of the insurance holder and are more likely to be siblings who were paired in error), indeterminate relationships in 32,116 (7%) pairs also warranted exclusion out of an abundance of caution due to the inability to determine the validity of the pair.

Figure 9. Value of variable indicating relationship to insurance holder for all linked pairs of females of childbearing age with members enrolled at birth who share family identification codes

Mother's Relationship to Insurance Holder	Infant's Relationship to Insurance Holder: Adopted child*	Brother/ Sister	Child	Child's Spouse	Grandson	Nephew/ Niece	Spouse's child	Other	Missing
Adopted child	0	0	1,116	0	65	0	0	3	0
Brother/Sister	0	0	79	0	0	3	0	0	0
Child	11	0	7,307	0	1,992	0	1	5	0
Child's spouse	0	0	3	0	141	0	0	0	0
Common-law wife	0	0	93	0	2	0	1	3	0
Foster parents	0	0	23	0	0	0	0	0	0
Grandson	0	0	0	0	5	0	0	0	0
Insured	2	0	19,299	0	353	5	0	1	152
Nephew/niece	0	0	11	0	0	0	0	0	0
Sister/brother in law	0	0	12	0	0	0	0	0	0
Spouse	16	1	381,333	1	746	1	4	30	2
Spouse's child	0	0	165	0	11	0	0	4	0
Spouse's parents	0	0	288	0	0	0	0	0	0
Younger brother/sister	0	0	317	0	1	13	0	0	0
Younger sister/brother in law	0	0	45	0	0	0	0	0	0
Parents	0	0	827	0	0	2	0	0	0
Other	0	0	368	0	57	0	0	12	0
Missing	0	0	14	0	0	0	0	0	31,465

	N	%
Assumed valid mother–infant pairs	400,730	89.8
Possible mother–infant pairs	2,225	0.5
Improbable mother–infant pairs	11,340	2.5
Unknown/missing relationships	32,116	7.2
Total	**446,411**	

Although some of the "adopted child" infant relationships could be valid relationships between mother and child, these are not valid mother–infant pairs for the purposes of studying *in utero* exposures.

Following restriction to only mother–infant linked pairs that possessed pregnancy or delivery codes (N = 300,703), the percentage of pairs that were confident matches increased to 93% (N = 278,225), and confident not mother–infant pairs were nearly eliminated (N = 34) (**Figure 10**). This observation supports that possible pairs with pregnancy or delivery codes were more likely to be valid mother–infant pairs, rather than invalid pairs.

Figure 10. Value of variable indicating relationship to insurance holder for linked pairs of females of childbearing age with members enrolled at birth who share family identification codes, restricted to those with pregnancy or delivery codes

Mother's Relationship to Insurance Holder	Infant's Relationship to Insurance Holder: Adopted child*	Brother/ Sister	Child	Child's Spouse	Grandson	Nephew/ Niece	Spouse's child	Other	Missing
Adopted child	0	0	2	0	37	0	0	1	0
Brother/Sister	0	0	1	0	0	2	0	0	0
Child	5	0	14	0	959	0	0	2	0
Child's spouse	0	0	0	0	92	0	0	0	0
Common-law wife	0	0	38	0	0	0	1	1	0
Foster parents	0	0	0	0	0	0	0	0	0
Grandson	0	0	0	0	0	0	0	0	0
Insured	0	0	17,196	0	1	0	0	1	140
Nephew/niece	0	0	0	0	0	0	0	0	0
Sister/brother in law	0	0	0	0	0	0	0	0	0
Spouse	4	1	260,986	0	4	0	4	8	1
Spouse's child	0	0	0	0	3	0	0	0	0
Spouse's parents	0	0	0	0	0	0	0	0	0
Younger brother/sister	0	0	2	0	0	9	0	0	0
Younger sister/brother in law	0	0	0	0	0	0	0	0	0
Parents	0	0	0	0	0	0	0	0	0
Other	0	0	28	0	39	0	0	9	0
Missing	0	0	2	0	0	0	0	0	21,110

	N	%
Assumed valid mother–infant pairs	278,225	92.5
Possible mother–infant pairs	1,102	0.4
Improbable mother–infant pairs	34	0.0
Unknown/missing relationships	21,342	7.1
Total	**300,703**	

Although some of the "adopted child" infant relationships could be valid relationships between mother and child, these are not valid mother–infant pairs for the purposes of studying *in utero* exposures.

Overall, this exercise in cross-referencing the relationships of the mothers and infants in each family identification code match allowed us to assess the assumed plausibility and supported an increased confidence in the validity of the mother–infant pairs. It is worth noting that, unfortunately, the JMDC documentation does not provide detail on the coding and use of this relationship variable (i.e., validity of the data field values, reasons for missingness) and therefore complete confidence in this assessment method is limited.

2.A.2.4. Consistency

The final element of data accuracy is data consistency, or the stability of a data value within a dataset. To assess consistency of the linked mothers and infants, we considered whether the data fields used for creation of the mother–infant pairs (i.e., family identification codes) were expected to be consistently used across the dataset. Unfortunately, as described above, our assessment was limited by the lack of detailed documentation from the JMDC regarding the

creation and use of the family identification variable. Useful information to assess the consistency here would include the date of inception of the current family identification coding version and whether this version covers the entire study period, such that assignment of codes would be expected to be consistent across all cohort members and over time.

2.A.3. Transparency of Data Processing

Observational research using real-world data has been criticized for lacking transparency in the details of the construction of the analytic cohort, which hinders the reproducibility of study results (i.e., the ability for independent researchers to obtain the same results when applying the same methodology to the same data source).[92] There are many opportunities throughout the research process to make decisions regarding study design features, and the ability to reproduce an epidemiologic study using real-world data relies on the clear reporting of these design decisions.[92, 93] Moreover, the unique demands involved with creating a novel mother–infant linkage in an administrative healthcare database require additional study parameter decisions to be made to link mothers and infants, which can further impede reproducibility. In our scenario, we considered whether the mother–infant pairs may be created via transparent data processing. Fortunately, we can publish our linkage algorithm (steps in the approach, codes used) with full transparency.

2.A.4. Provenance

Finally, data provenance describes the origin of the data (as data move from the point of collection into the database). In our scenario, we considered whether processes of the data collection and database creation and preparation may have impacted the quality of the mother–infant matches. This analysis was limited by the lack of detailed information regarding the actions of the vendor in terms of potential transformations performed on the family identification variable, but we have been informed that the JMDC does not perform any transformation processes to this variable after receiving the data from the payers.

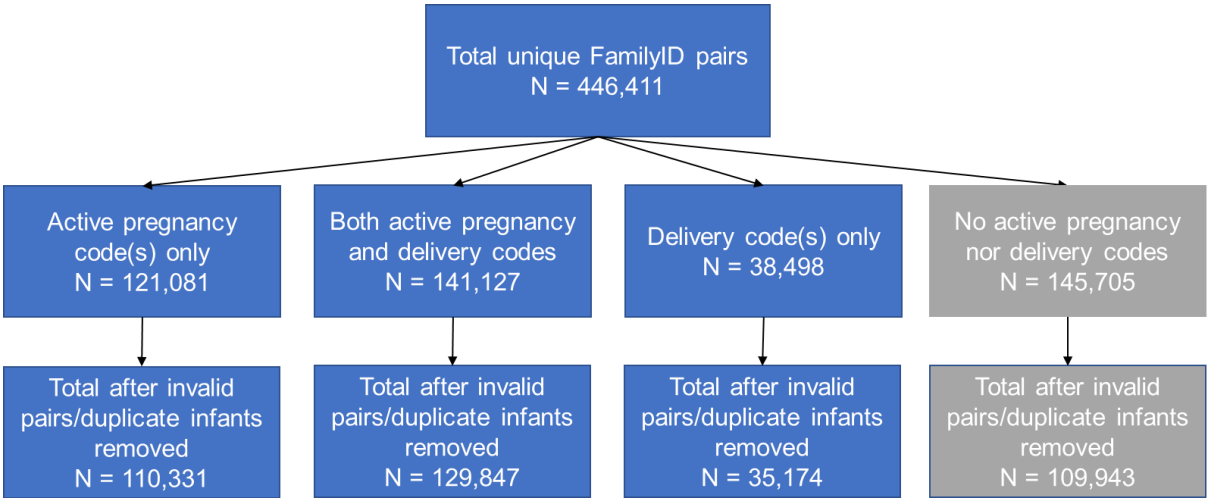
2.B. Gestational Period

Healthcare claims also do not inherently indicate pregnancy timing (e.g., estimated date of conception) and therefore this information must be reconstructed by researchers to allow for pregnancy target trial emulation.[35-45] Consideration of whether a linked cohort of mothers and infants in the JMDC claims database is fit for regulatory use involved assessment of the quality of this gestational age estimation.

2.B.1. Completeness

The completeness of the data relates to the extent and potential mechanisms of missingness. Here, we considered whether information on the gestational period was expected to be available for the complete linked population. Complete information on infant date of birth is not available in the JMDC claims database. The JMDC reports only month and year of birth, removing the day to avoid the possibility of re-identification, meaning that estimation of infant date of birth is required according to maternal records of delivery date. As date of delivery is also not available in Japanese claims, delivery date/infant date of birth must be estimated according to diagnoses and procedures that indicate delivery, which do have associated dates available.[94] Delivery is not necessarily always covered by the Japanese National Health Insurance System. When a delivery does not require any surgical procedures or medications that are covered by the health insurance, information regarding the delivery would not be reported to the health insurance system. Our examination of the presence of pregnancy and/or delivery codes among valid mother–infant pairs according to Linkage Method B revealed that 57% of valid pairs lacked delivery codes (**Figure 11**). In this case, the 15th day of the infant birth month, for example, would need to be inserted as an estimated delivery date.

Figure 11. Assessment of pregnancy and delivery coding among mother–infant linkages in the JMDC claims database



Following the estimation of delivery date, gestational age would also need to be estimated to back calculate an estimated pregnancy onset date (to allow for the correct designation of exposure windows and cohort entry). Estimation of gestational age in mother–infant claims linkages has previously been performed, and algorithms are available in the literature.[36, 42, 65] These algorithms often employ codes related to pregnancy milestones, which may also be limited in this cohort due to the observation that 38% of valid mother–infant pairs did not have any codes indicating an active pregnancy (**Figure 11**). In this situation, the gestational length of a term pregnancy may be imputed as a best guess, such that pregnancy onset date would be non-missing for the entire linked population (although this may compromise accuracy, as described in more detail below). Notably, dual imputation of delivery date and impaired estimation of gestational age is expected to be required in 29% of valid pairs for which both delivery and pregnancy codes were missing.

2.B.2. Accuracy

The next data quality element is related to whether the estimation of the gestational period was expected to be accurate. This assessment involved consideration of the validity, logical plausibility, and consistency of the data.

2.B.2.1. Validity

As previously described, validity is a measure of concordance between a data field and a definitive measure. In this scenario, we considered whether the estimated gestational period is expected to reflect the true gestational period for each mother–infant pair. Inserting an estimated delivery date and gestational age for each mother–infant pair is expected to result in some mismeasurement, such that the assignments will not match the truth for some subset of pairs. Gestational timing information is vital for studying medication safety during pregnancy because fetal developmental timelines mean that there are specific windows of time during which exposures could cause specific congenital malformations.[47] For example, exposures during the first trimester may cause cardiac malformations, due to the timing of fetal heart development, but exposures occurring later in pregnancy are unlikely relevant to this system. In a hypothetical randomized trial of medication safety during pregnancy on the risk of cardiac malformations, enrollment and exposure randomization would be anchored around this critical first trimester exposure window.

Misclassification of the exposure window could arise in many ways in this cohort due to the limitations of gestational age validity. **Figure 12** displays the estimated first trimester exposure window relative to the true first trimester exposure window when delivery and pregnancy timing information is available versus imputed, for term, preterm, and post-term deliveries.

Figure 12. Comparison of true first trimester exposure window with that estimated in the JMDC under various scenarios according to the availability of pregnancy and delivery codes

[1] Term delivery is defined here as 273 completed gestational days.
[2] When delivery code is missing, delivery date/infant date of birth is imputed as the fifteenth day of the infant birth month.
[3] When pregnancy code is missing, gestational age is imputed as the length of a term birth (273 days).
[4] Preterm delivery is defined here as 245 completed gestational days, but could be as short as 168 days.
[5] Post-term delivery is defined here as 287 completed gestational days, but could be a long as 294 days.

Reassuringly, for term deliveries (**Figure 12A–D**), which represent 94% of deliveries in Japan, even when both delivery codes and pregnancy codes indicating gestational timing are missing, the maximum exposure window misclassification results in a 15-day shift (which, compared to a 90-day trimester, means that ≥85% of the true exposure window is covered by the estimated window). Exposure window misclassification is the worst for preterm deliveries that are missing codes indicating gestational timing (**Figure 12G–H**) as imputing a gestational length of 273 days for these pregnancies causes the first trimester exposure window to be shifted earlier in time. For a preterm birth with true gestational length of 245 days, imputing a term length would shift the exposure window 28 days earlier, causing 69% coverage of the true exposure window (**Figure 12G**). This overestimation of pregnancy start date worsens for extremely preterm births; a true gestational length of 168 days would result in the estimated exposure window shifting forward 105 days, which would miss the true exposure window completely. An additional forward shift of 15 days could occur if an infant was born on the 30th day of the month, but missing delivery codes require imputation of the 15th day of the month as the delivery date (**Figure 12H**). Finally, for post-term deliveries (**Figure 12I–L**), missing gestational length information causes a shorter than true gestational age to be imputed, shifting the estimated exposure window later in time relative to the truth. In the worst-case scenario, where both gestational age and delivery information are missing (**Figure 12L**), the estimated exposure window could be shifted up to 36 days later, resulting in only 60% coverage of the true exposure window. It is possible that misclassification of the exposure window could be associated with infant congenital malformation status (i.e., differential exposure misclassification) if there are shared mechanisms for congenital malformations and preterm birth. For example, it has been reported that preterm birth occurs more commonly among infants with cardiac malformations (23%) compared to those without (8%), which would result in greater exposure window misclassification rates among those with the outcome.[95, 96]

2.B.2.2. Conformance

Another element of data accuracy is conformance, which describes whether the data are congruent with standardized types, sizes, and formats. In this scenario, we considered whether the information required to estimate gestational period (i.e., delivery and pregnancy codes) conforms with the standardized format. Japan uses ICD-10 codes that are congruent with the international standard. However, the JMDC does not support the fifth level digit of the code (where gestational week information is available), which is inconsistent with the standard availability in other claims databases. This lack of fifth level ICD-10 coding occurs because the JMDC standardizes diagnosis data using a linkage list between ICD-10 codes and standard disease names (unique to Japan) published by the Japanese government. In this linkage list, the ICD-10 fifth level is not available, and therefore the ICD-10 diagnosis codes in the JMDC claims database are limited to the fourth level. Furthermore, a series of ICD-10 Z3A codes are standardly used to specify the week of gestation in the fourth and fifth digits (e.g., Z3A29 indicates 29 weeks of gestation), but are unavailable in the Japanese system. This limits our ability to finely estimate gestational age based on ICD-10 codes available in the JMDC claims database. **Table 10** displays the translation of a gestational age algorithm defined in MarketScan using ICD-9 codes into ICD-10 codes as they are available in the JMDC claims database. The first four hierarchical steps in the MarketScan algorithm, which employ four different ICD-9 codes to assign gestational ages between 168 and 196 days, become collapsed into a single ICD-10 code (P07.2) in the JMDC claims database. A similar phenomenon occurs for steps 4 through 11, which assign gestational ages between 196 and 245 days. Finally, steps 13 through 16 differentiate between post-term births under 42 weeks (287 days) and over 42 weeks (294 days), which is not possible in the JMDC claims database. It is worth noting that, in many cases, the fifth level digit of the ICD-10 codes would have allowed for even finer discrimination of gestational weeks compared to the codes in the previous ICD-9 version.

Table 10. Mapping of ICD-9 gestational age algorithm to the Japan Medical Data Center (JMDC) ICD-10 availability

	MarketScan Linkage Algorithm			ICD-10 Mapping		JMDC Availability	
Step	ICD-9 Code	Description	Estimated Gestational Age (Days)	ICD-10 Code	Description	ICD-10 Code	Description
1	765.21	<24 completed weeks	168	P07.21	Extreme immaturity of newborn, <23 completed weeks	P07.2	Extreme immaturity (<28 weeks)
				P07.22	Extreme immaturity of newborn, 23 completed weeks		
2	765.22	24 completed weeks	168	P07.23	Extreme immaturity of newborn, 24 completed weeks	P07.2	Extreme immaturity (<28 weeks)
3	765.23	25–26 completed weeks	182	P07.24	Extreme immaturity of newborn, 25 completed weeks	P07.2	Extreme immaturity (<28 weeks)
				P07.25	Extreme immaturity of newborn, 26 completed weeks		
4	765.24	27–28 completed weeks	196	P07.26	Extreme immaturity of newborn, 27 completed weeks	P07.2	Extreme immaturity (<28 weeks)
				P07.31	Preterm newborn, 28 completed weeks	P07.3	Other preterm infants (after 28 weeks)
5	765.0–765.09	Extreme immaturity	196	P07.0–P07.03	Extremely low birth weight newborn	P07.0	Extremely low birth weight
				P07.1–P07.18	Other low birth weight newborn	P07.1	Other low birth weight
				P07.30	Preterm newborn, unspecified weeks	P07.3	Other preterm infants (after 28 weeks)
6	765.25	29–30 completed weeks	210	P07.32	Preterm newborn, 29 completed weeks	P07.3	Other preterm infants (after 28 weeks)
				P07.33	Preterm newborn, 30 completed weeks		
7	765.26	31–32 completed weeks	224	P07.34	Preterm newborn, 31 completed weeks	P07.3	Other preterm infants (after 28 weeks)
				P07.35	Preterm newborn, 32 completed weeks		
8	765.27	33–34 completed weeks	238	P07.36	Preterm newborn, 33 completed weeks	P07.3	Other preterm infants (after 28 weeks)
				P07.37	Preterm newborn, 34 completed weeks		
9	765.28	35–36 completed weeks	252	P07.38	Preterm newborn, 35 completed weeks	P07.3	Other preterm infants (after 28 weeks)
				P07.39	Preterm newborn, 36 completed weeks		
10	765.1–765.19	Other preterm infants	245	P07.0–P07.03	Extremely low birth weight newborn	P07.0	Extremely low birth weight
				P07.1–P07.18	Other low birth weight newborn	P07.1	Other low birth weight
				P07.30	Preterm newborn, unspecified weeks	P07.3	Other preterm infants (after 28 weeks)
11	765.20	Preterm with unspecified weeks	245	P07.20	Extreme immaturity of newborn, unspecified weeks	P07.2	Extreme immaturity (<28 weeks)
				P07.30	Preterm newborn, unspecified weeks	P07.3	Other preterm infants (after 28 weeks)
12	644.21	Onset of delivery before 37 completed weeks	245	O60.12X0	Preterm labor second trimester with preterm delivery second trimester, not applicable or unspecified	O60.1	Preterm spontaneous labor with preterm delivery
				O60.13X0	Preterm labor second trimester with preterm delivery third trimester, not applicable or unspecified		
				O60.14X0	Preterm labor third trimester with preterm delivery third trimester, not applicable or unspecified		
13	645.1x	Post-term pregnancy, delivered, with or without mention of antepartum condition (>40 to 42 completed weeks)	287	O48.0	Post-term pregnancy	O48-	Prolonged pregnancy
14	766.21	Post-term infant (>40 to 42 completed weeks)	287	P08.21	Post-term newborn	P08.2	Post-term infant, not heavy for gestational age
15	645.2x	Prolonged pregnancy, delivered (>42 completed weeks)	294	O48.1	Prolonged pregnancy	O48-	Prolonged pregnancy
16	766.22	Prolonged gestation (>42 completed weeks)	294	P08.22	Prolonged gestation of newborn	P08.2	Post-term infant, not heavy for gestational age
17	NA	Without any of the codes for pre-term or post-term	273	NA	Without any of the codes for pre-term or post-term	NA	Without any of the codes for pre-term or post-term

2.B.2.3. Logical Plausibility

Data accuracy also implies that the recorded values are logically believable given data source and expert opinion. In other words, whether the estimated gestational period reflects a logically plausible gestational period for all mother–infant pairs. As previously mentioned, methods from the literature could be used to insert an estimated gestational age for each mother–infant pair.[36, 42, 65] For example, a fixed duration of 35 weeks may be assigned to all preterm births and a fixed duration of 40 weeks to all non-preterm births (which is based on the median gestational ages for these two groups).[42] Because of this, it will be guaranteed that there are no logically implausible gestational ages (i.e., gestational age greater than post-term or less than the length of a viable live birth).

2.B.2.4. Consistency

The final element of data accuracy is data consistency, or the stability of a data value within a dataset or across linked datasets. In this scenario, we considered whether the information that will be used to estimate gestational period (i.e., pregnancy and delivery codes) is consistently used across all individuals. We do expect the use of pregnancy and delivery codes to be consistent across all mothers in the linked cohort as the current ICD-10 coding scheme has been in use in Japan since 1990, and therefore covers our entire study period.

2.B.3. Transparency of Data Processing

Our assessment of the quality of the gestational age estimation also considered whether the gestational period may be estimated via transparent data processing. As stated above for the creation of the mother–infant matches, we will be able to publish an algorithm for gestational period estimation (steps in the approach, codes used) with full transparency.

2.B.4 Provenance

Finally, data provenance describes the origin of the data (as data move from the point of

collection into the database). Provenance may involve processes of data recording and transformations as performed by the vendor. In our scenario, we considered whether processes of the data collection and database creation and preparation may impact the quality of the data elements involved in gestational age estimation. As described above, the way in which the JMDC standardizes diagnosis data from standard disease names (unique to Japan) to ICD-10 diagnosis codes using a linkage list published by the Japanese government limits the maximum unit of ICD-10 information to the fourth level. This is expected to impact the quality of the gestational age estimation as coding of specific gestational week is not available.

Summary of Assessment

A summary of our assessment of the fitness for regulatory purpose of a linked cohort of mothers and infants in the JMDC claims database, within the context of estimating infant major congenital malformations associated with *in utero* exposure to marketed medications, according to the data considerations as outlined by the Duke-Margolis framework, is provided in **Table 11**.

Table 11. Duke-Margolis framework for data fitness for purpose applied to the Japan Medical Data Center (JMDC) claims database mother–infant linked cohort

Data Element	Considerations	Findings
Data Relevancy		
Availability of Key Data	Whether critical data fields required to address the research question are available: the exposure (maternal medication exposure), the outcome (infant major congenital malformations), potential covariates of interest, and data fields permitting accurate patient-level mother–infant linkage.	• Data fields for exposure, outcome, and potential covariates of interest were used to generate descriptive statistics and were expected to be complete. • Data fields for patient-level mother–infant linkage were used in Linkage Methods A and B.
Representativeness	Whether the patients in the linked mother–infant JMDC population are expected to be representative of the population of interest (i.e., pregnant people in Japan and their liveborn infants).	• Comparison to publicly available data from Japan suggested preterm births were under-recorded in this population (3.6% versus 5.6%). • Total congenital malformations were over-represented in this population compared with the general Japan population (10.8% versus 5.3%), but the prevalence of each specific subtype was mostly consistent. • Maternal characteristics appeared mostly consistent with the population of same-aged females in Japan.

Data Element	Considerations	Findings
Sufficient Subjects	Whether the linked population of mothers and infants is expected to be sufficiently large, with sufficient outcome events among the infants.	• 385,295 total valid mother–infant pairs were identified, representing about 2% of live births in Japan during the study period. • About 41,000 total infant congenital malformations were observed among these pairs. • The prevalence of specific maternal medication exposures and infant congenital malformations varied widely, suggesting sufficient populations may be available to precisely estimate some, but not all, exposure–outcome associations.
Longitudinality	Whether the mothers are continuously enrolled for the entire pregnancy and the infants are under follow-up for a sufficient timeframe to observe outcomes.	• 57% of mothers from valid pairs were continuously enrolled during pregnancy. • 86% of infants form valid pairs had at least a year of follow-up. • 49% of valid pairs met both pregnancy and follow-up continuous enrollment.
Data Quality (Mother–Infant Matches)		
Completeness	Whether the mother–infant linkage process is expected to identify the complete set of mothers and infants in the JMDC.	• The linkage rate was 56% for pregnancy episodes that had codes indicating a live birth delivery. • Of the annual live births captured in the JMDC, we found that 54% were able to be linked to a mother. • These linkage rates align with expectations of the proportion of infants who would be covered under their mother's, versus other parent's, health insurance plan.
Accuracy	Validity: Whether the family identification variable is a valid indicator of family relation.	• Family identification codes are generated and used for billing purposes and therefore expected to correctly indicate correspondence between insured individuals and their dependents.
	Conformance: Whether the family identification variable is congruent with standardized types, sizes, and formats.	• Family identification codes are always assigned, regardless of the presence or number of dependents corresponding to an insured individual, and are never missing. • The creation and maintenance of the claims database itself does not disrupt family identification information.
	Logical Plausibility: Whether the "mothers" and "infants" who have been linked together are plausible mother–infant pairs.	• Cross-tabulation of values indicated for the relationship of the "mother" and "infant" to the insurance holder allowed for confirmation of assumed mother–infant relationships in 90% of pairs. • Exclusion of invalid and indeterminate matches strengthened our confidence in the validity of mother–infant pairings.
	Consistency: Whether the data fields used for creation of the mother–infant pairs (i.e., family identification codes) are expected to be consistently used across the dataset.	• There was a lack of detailed documentation from the JMDC regarding the creation and use of the family identification variable.
Transparency of Data Processing	Whether the mother–infant pairs may be created via transparent data processing.	• Full transparency of the linkage algorithm is achievable.
Provenance	Whether processes of the data collection and database creation may impact the quality of the mother–infant matches.	• The JMDC does not perform any transformations to the family identification variable after receiving the data from payers.

Data Element	Considerations	Findings
Data Quality (Gestational Period Estimation)		
Completeness	Whether information on the gestational period is expected to be available for the complete linked population.	• The JMDC reports only month and year of birth, removing the day to avoid the possibility of re-identification. • 60% of valid pairs lacked a delivery code, meaning that delivery date/infant date of birth would need to be imputed. • 41% of valid pairs did not have any codes indicating an active pregnancy, which would hinder the ability to estimate gestational age.
Accuracy	Validity: Whether the estimated gestational period is expected to reflect the true gestational period for each mother–infant pair.	• Estimations of delivery date and gestational age are expected to result in misclassification of the exposure window, the degree of which varies by preterm versus term status.
	Conformance: Whether information that will be used to estimate gestational period (i.e., codes) is congruent with standardized types, sizes, and formats.	• The JMDC does not support the fifth level digit of the ICD-10 codes (where gestational week information would have been available), which is inconsistent with the standard availability in other claims databases and would limit the ability to finely estimate gestational age.
	Logical Plausibility: Whether the estimated gestational period reflects a logically plausible gestational period for all mother–infant pairs.	• Methods from the literature could be used to insert an estimated gestational age for each mother–infant pair, which would guarantee that there are no gestational ages greater than post-term or less than the length of a viable live birth.
	Consistency: Whether the information that will be used to estimate gestational period (i.e., codes) is consistently used across all individuals.	• Pregnancy and delivery coding are expected to be consistent across all mothers in the linked cohort as the current ICD-10 coding scheme has been in use in Japan since 1990.
Transparency of Data Processing	Whether the gestational period may be estimated via transparent data processing.	• Full transparency of the gestational age algorithm is achievable.
Provenance	Whether processes of data collection and database creation and preparation may impact the quality of the data elements involved in gestational age estimation.	• The way in which the JMDC standardizes diagnosis data from standard disease names to ICD-10 limits the maximum unit of ICD-10 information to the fourth level.

Discussion

In this analysis, we have employed two linkage methods and examined descriptive characteristics to assess whether a linked cohort of mothers and infants in the JMDC claims database is fit for regulatory use within the context of estimating infant outcomes associated with *in utero* exposure to marketed medications. We assessed a series of data considerations related to the relevancy and quality of the database, as outlined according to the Duke-Margolis

framework for fit-for-purpose real-world data evaluation.[25] Although complete and accurate identification of mothers and their liveborn infants who share a health insurance plan was possible, allowing for the creation of a large mother–infant cohort with detailed information regarding prescription dispensing during pregnancy, the limitations of gestational age information may impede the valid assignment of pregnancy onset and delivery dates as needed to define critical *in utero* exposure windows. These results suggest that additional research is needed to identify gestational age in this database before proceeding with pregnancy safety research to inform regulatory decision-making.

Relevancy relates to capacity to answer the research question, in terms of availability of critical data fields and a sufficiently sized, representative population. In terms of relevancy, we determined that critical data fields (maternal medication exposures, infant major congenital malformations, covariates) were available. Family identification codes permitted patient-level mother–infant linkage. 385,295 total mother–infant pairs were identified, representing about 2% of live births in Japan during the study period. About 41,000 congenital malformations were observed among these pairs. It appears that a sufficiently sized population, in terms of expected precision of estimates, would be available to study associations between some maternal medication exposures (e.g., anti-diabetics, anticonvulsants, or SSRIs) and congenital malformations (e.g., congenital heart anomalies, congenital musculoskeletal and limb anomalies) that occurred more commonly in this population, yet not for others that occurred more rarely. 57% of mother–infant pairs involved a mother with continuous enrollment during pregnancy and 86% had at least one year of infant follow-up; 49% met both pregnancy and follow-up continuous enrollment. In Japan, all individuals are covered under the National Health Insurance system. Additionally, pregnancy-related care is covered under a government-subsidized maternity voucher program. As a result, it is unexpected that a pregnant person in Japan would have any gaps in their continuity of care and therefore we expect that the low

continuous enrollment rates observed in this cohort may be more reflective of how care is captured by the database rather than how care is received for this population. Future studies may further investigate the continuous enrollment timing in this cohort, examining whether the linked females are losing their insurance coverage at the beginning of the fiscal year (indicating that their employer may have changed their contract with the JMDC data vendor) or at random (indicating that the female has changed insurance plans). Regardless of the source of the low continuous enrollment, if future pregnancy safety studies using this cohort were to require continuous enrollment during pregnancy, sample size and expected precision of estimates may be compromised due to exclusion of nearly half of the valid pairs.

Comparison to publicly available data from Japan suggested total major congenital malformations were over-represented (10.8% versus 5.3%) in this population. Previous analysis in the JMDC claims database by Ishikawa et al. reported a prevalence of major congenital malformations of 5.3%, although the ICD-10 algorithms differed slightly those of the present analysis, especially for the category of “other” major congenital malformations.[44, 45] In our cohort, exclusion of “other” congenital birth defects from the total major congenital malformation prevalence attenuated the observed over-representation of major congenital malformations in the JMDC (5.5%). It is not clear whether this over-representation, which is apparently driven by “other” congenital birth defects, is due to over-reporting of congenital abnormalities in the linked JMDC population (i.e., outcome misclassification, likely driven by alternative and minor congenital malformations being inadvertently lumped in with the catch-all “other” category) or if there is truly a higher prevalence of congenital abnormalities in this insurance population. For example, the members of the JMDC insured group are individuals with insurance through their employer, plus dependents, and therefore may represent a population at higher risk of congenital abnormalities compared with the general population (e.g., higher exposure to workplace hazards related to the risk of congenital abnormalities). Even if the higher proportion

of congenital abnormalities in the JMDC population, compared with the general population, is due to outcome misclassification (i.e., greater sensitivity), any such inaccuracy is unlikely to differ between those who were and were not exposed to prescription medications use during pregnancy (i.e., non-differential with respect to exposure). It is also unlikely that infants without congenital abnormalities would be reported as cases (i.e., specificity of the outcome is expected to be perfect or nearly perfect). In general, when specificity is perfect and sensitivity for the exposed and unexposed groups are equal, ratio measures of association are unbiased. Future studies may seek to confirm a known causal association between a medication exposure during pregnancy and infant congenital malformations in this cohort to assess the validity of outcome ascertainment and the ability to produce unbiased results.[97]

Maternal characteristics appeared mostly consistent with the population of same-aged females in Japan. The prevalence of several chronic conditions (anxiety disorders, asthma, major depressive disorder, migraine), as well as maternal hypertensive disorders, increased when the JMDC linked population was restricted to those with pregnancy or delivery codes, as compared with the total linked population, indicating that those with chronic conditions may be more likely to interact with the healthcare system during pregnancy in a way that will generate claims. The population of unlinked mothers, compared to linked mothers, were more likely to have most of the medical conditions examined, but the prevalence of medication use was similar for the two populations across all medication classes examined. Finally, preterm births were under-recorded (3.6% versus 5.6%) in this population. The gestational age at which an infant is born is associated with a variety of maternal characteristics (e.g., age at pregnancy, comorbid conditions, lifestyle factors, multiple pregnancy), as well as the infant's risk of mortality and morbidity.[98, 99] Given the observed over-representation of major congenital malformations in this cohort, this under-representation of preterm birth is unexpected; major congenital malformations are associated with an increased risk of preterm birth and therefore a greater prevalence of

preterm birth would have been expected in conjunction with the increased prevalence of major congenital malformations.[100, 101] Furthermore, as preterm births may be more likely to accompany pregnancies and deliveries requiring medical intervention, we would have expected the JMDC claims database to have an over-representation of preterm birth given the policies for delivery coverage in the Japan National Health Insurance System. The observed lower prevalence of preterm birth in this population could be due to coding practices in the healthcare system or could be a true lower preterm birth prevalence in this privately employed population (e.g., socioeconomic characteristics).

Quality relates to ability to validly answer the research question, in terms of data completeness, accuracy, and transparency. In terms of quality, our methods were expected to accurately identify the complete set of mothers and infants in the JMDC enrolled in a shared health insurance plan. Females with evidence of a live birth delivery, as well as infants enrolled in a JMDC-covered plan in their birth month, had linkage rates of about 50%, which align with expectations of infant insurance coverage under the mother's, versus other parent's, plan. Cross-tabulation of values indicated for the relationship of the "mother" and "infant" to the insurance holder allowed for confirmation of assumed biologic mother–infant pairs in 90% of all presumed mothers and infants matched via family identification codes. Exclusion of invalid and indeterminate matches (which resulted in a 14% reduction in the initially matched pairs; from 446,411 to 385,295) was intended to strengthen our confidence in the validity of mother–infant pairings.

The completeness and accuracy of gestational age information was limited given the lack of live birth delivery codes for 60% of the cohort and missing pregnancy-related codes for 41% of the cohort. Although linkage of mothers and infants based on family identification codes (Linkage Method B) bypasses dependence on pregnancy and live birth delivery codes to identify mothers (Linkage Method A), missing delivery date and pregnancy timing information, coupled with

suppression of infant birth dates and inaccessibility of ICD-10 codes with fifth level digits (where gestational week information would have been available) in the database, limits the ability to finely estimate gestational timing, and therefore critical exposure windows, as needed for regulatory post-approval pregnancy safety studies. The magnitude of potential exposure window misclassification in this cohort is difficult to quantify, as it could arise in many ways. For pregnancies with missing delivery date and gestational age information, these data would need to be imputed. The fifteenth day of the infant birth month may be used as an estimated delivery date, and a term gestational age may be used to estimate the pregnancy start date. The method of imputing a term gestational age for those without a preterm status indicator has previously been used in the literature, but does assume preterm status to be accurately and completely indicated in the claims database, which may not be the case in the JMDC claims database given the observed underrepresentation of preterm birth status.[36, 42, 65] We suspect that for the majority (94%) of pregnancies, which involve term deliveries, missing delivery and gestational timing information is expected to result in only minor shifts of the exposure window such that most of the true exposure window is still covered by the estimated window. Additional fluctuations in delivery timing relative to the average length of term pregnancies may introduce further shifts to the estimated exposure window. Many pregnancy safety studies define exposure according to “ever” versus “never” use, either during any time in pregnancy or during each specific trimester. Claims-based algorithms have been found to have high positive (>96%) and negative (>99%) predictive values for classification of chronic medication exposures with this type of binary definition.[102] If medication use status throughout pregnancy is expected to be constant, then this type of binary exposure definition would be expected to perform well, even in the face of a shifted exposure window. The most concerning scenario, however, occurs when a preterm birth lacks codes related to both delivery and gestational timing, which could cause the estimated exposure window to be shifted so much as to have no overlap with the true exposure window for extremely preterm births. This possibility is particularly of concern given that many

people cease or change prescription medication use when they learn that they are pregnant; prescription use as measured in the pre-pregnancy period likely will not accurately reflect first trimester exposures for medications not related to chronic conditions.[96, 103] The magnitude and directionality of bias introduced due to misalignment of the estimated and true exposure windows depends on the specific research question of interest. For example, for a first trimester critical exposure window, shifting the exposure assessment window earlier in time means that exposure status will be measured before the true pregnancy has begun. This may result in either imperfect sensitivity of the exposure for medications with known teratogenic effects that are likely to be ceased upon the start of pregnancy or imperfect specificity of the exposure for medications likely to be initiated during the first trimester (e.g., medications to treat pregnancy-related nausea and vomiting).[104, 105] Alternative outcomes with different critical exposure windows (e.g., third trimester) will result in a different set of potential bias considerations. It is possible that estimation of gestational timing and the resulting exposure windows could be related to infant congenital malformation status (i.e., non-differential exposure misclassification), for example if those with congenital malformations are more likely to be born preterm.[95, 96] Additionally, socioeconomic factors are likely to be related to access to care and medication use during pregnancy, as well as the risk of major congenital malformations.[106-109]

This analysis is not without limitations. First, it is important to note that the Duke-Margolis framework sets forth a list of considerations for assessing fitness for purpose of real-world data, but does not specify analysis plans nor provide quantitative thresholds for determining whether each relevancy and quality dimension is met. Our assessment here was therefore based on our own interpretation of the framework and our translation of the various dimensions into descriptive epidemiologic research questions based on our scientific and regulatory context. It is important to acknowledge that alternative assessment methods for each dimension could have been possible. However, communication with experts in the field of pregnancy safety, as well as

those familiar with Japan's healthcare system and the JMDC database, helped to inform our chosen analyses.

Next, our analysis identified pregnancy and delivery episodes based on diagnosis codes alone. It is possible that additional episodes could have been identified via incorporation of medical and surgical procedure codes. Previous work in the JMDC database also incorporated prescribed medications during hospitalizations likely to be associated with delivery.[44, 45, 94] Addition of procedures and prescribed medications to the delivery algorithm could result in reduction of the proportion of females without a delivery date based on live birth diagnosis codes alone (60%). It is not clear how often females would have a procedure coded during delivery in the absence of an accompanying diagnosis, and therefore we are unable to comment on the potential change to the proportion with an estimable delivery date due to the incorporation of delivery-related procedures. Future research may examine the impact of including procedures and medications on the delivery date and gestational age estimation.

Additionally, in this analysis, Linkage Method A allowed us to observe the linkage rate to be 56% for pregnancy episodes with evidence of a live birth delivery. The unlinked mothers in this scenario appear to correspond with expectations of infants being enrolled as dependents on their mother's, versus other's parents, insurance plan about half of the time. In comparison, the linkage rate was only 40% for pregnancy episodes identified according to codes indicating an ongoing, active pregnancy, which may not necessarily have ended in a live birth. The unlinked pregnant people in this scenario are expected to be a combination of (a) mothers whose liveborn infants are covered by a different health insurer, (b) pregnant people whose pregnancy ended in a spontaneous abortion or stillbirth, and (c) females who did not experience a pregnancy during the study period. It is important to understand unlinked females who are mothers who experienced a live birth delivery (part of the target population of all mothers and their liveborn infants in Japan) versus those who did not to understand how well this linked

cohort can represent the target population. Future research should query the unlinked females for diagnosis codes indicating the occurrence of spontaneous abortion and stillbirth to better understand this distribution of females in the JMDC population.[110] Japanese Vital Statistics include required reporting of fetal deaths, which could serve as a comparison to the rates observed among the JMDC population.[68]

Finally, this fit-for-purpose real-world data evaluation was limited by the information available from the data vendor. Our mother–infant pairs were created according to values indicated for the family identification and relationship to the insurance holder variables. Unfortunately, there is a scarcity of detailed information available from the JMDC regarding these variables, including potential for miscoding and reasons for missingness. Given that the family identification codes are used to identify relations between insurance plan holders and dependents for the purposes of billing, we expect these values (which are always non-missing) to be correctly coded. The accuracy of the relationship variable, however, is less clear given that insurance benefits are provided to all dependents, regardless of specific familial relationship, so there is less motivation from the billing viewpoint for this variable to be valid and non-missing.

Overall, results suggest the JMDC claims database may be well-suited for descriptive studies of pregnant people in Japan (e.g., comorbidities, medication usage). More work is needed to identify a method to assign pregnancy onset and delivery dates so that *in utero* exposure windows can be defined more precisely as needed for many regulatory postapproval pregnancy safety studies.

CHAPTER 3: REAL-WORLD RISK OF SEVERE CYTOPENIAS IN MULTIPLE MYELOMA PATIENTS SEQUENTIALLY TREATED WITH IMMUNOMODULATORY DRUGS

Abstract

Background: Most multiple myeloma (MM) patients experience myelosuppression due to both underlying disease and treatment. Cytopenias are most commonly associated with regimens containing immunomodulatory agents (IMiDs). Most MM patients relapse and subsequent regimens could include IMiDs. The impact of sequential IMiD treatment on severe cytopenia risk is unknown, as studies have not examined risk across multiple lines of therapy (LOTs).

Objective: To evaluate the risks of severe cytopenias in relapsed MM patients who received sequential IMiD treatment versus IMiD-free regimens.

Methods: The Flatiron Health database contains de-identified electronic health records from patients treated at ~280 United States cancer clinics. Patients ≥18 years diagnosed with MM between 01 January 2011 and 31 December 2020 who received at least two LOTs were included. Four exposure groups were created according to whether IMiDs were received during LOTs 1 or 2. Those for which both LOTs contained IMiDs were considered “sequentially exposed”; those for which neither contained IMiDs were “never exposed.” Follow-up was from initiation of LOT 2 until the earliest of the outcome (grade 3 or 4 cytopenias, according to the Common Terminology Criteria for Adverse Events version 5.0), death, LOT end, or study end (31 December 2021). Inverse probability of treatment weighting models included age, diagnosis year, sex, race, body mass index, practice type, insurance type, region, stage, cytogenetic risk, pre-existing comorbidities, treatment history, prior maintenance therapy, relapse timing, and recent cytopenia history (≤90 days from LOT 2 start). Cumulative risks up to 12 months were estimated for each exposure group and risk differences (RD) were calculated. Analyses were repeated stratified by recent cytopenia history, age, and cytogenetic risk.

Results: The cohort included 5,573 MM patients. Most (N = 2,082) were sequentially exposed

to IMiDs, with only 974 never exposed. Compared to those never exposed, those sequentially exposed were on average younger (mean 65 vs 69 years), diagnosed at a lower stage (ISS I 24% vs 14%) and in later years (≥2016 47% vs 30%), had a better performance status (ECOG ≤1 43% vs 33%), and had longer time to relapse (≥24 months 20% vs 13%). The cumulative risk of neutropenia at 1 year was substantially higher among those exposed versus unexposed to IMiDs at LOT 2 (21% [95% confidence interval [CI] 19%, 23%] vs 13% [95% CI 12%, 15%]) and stratification on prior IMiD exposure revealed a trend in which, compared to those never exposed, those sequentially exposed had the highest 1-year risk (RD 12% [95% CI 9%, 15%]), followed by those only recently exposed during LOT 2 (RD 8% [95% CI 4%, 11%]), then by those with only past exposure during LOT 1 (RD 5% [95% CI 1%, 8%]). A similar pattern was observed for leukopenia. In contrast, the 1-year risks of anemia, lymphocytopenia, and thrombocytopenia were similar among those treated with, versus without, IMiDs at LOT 2. Stratification on prior IMiD exposure did not meaningfully change the risks of anemia or lymphocytopenia, but did suggest an increased risk of thrombocytopenia among those receiving IMiDs at either or both LOT, versus never exposed.

Risks of all severe cytopenias were substantially lower among those with no recent cytopenia history. The associations between sequential, versus never, exposure with leukopenia and neutropenia were even stronger among those with a history of the given cytopenia, but were attenuated for those with no history. Risks for cytopenias not related to white blood cells (anemia, thrombocytopenia) among those with no recent history did not exceed 10%, even for those sequentially exposed.

Conclusions: Results suggest sequential exposure to IMiDs across two LOTs to be mainly of concern for risk of severe cytopenias related to white blood cells, particularly neutrophils, and especially among those with recent histories. Although adverse events due to cytopenias, such as infections, could not be accurately ascertained in this study, results suggest administering an IMiD-free regimen following an IMiD regimen may reduce severe cytopenia risk.

Background

Although useful for efficient pharmacoepidemiologic research, real-world data, by virtue of being collected as a part of routine healthcare processes, rather than from regimented clinical trials, do not involve random allocation of treatment to individuals. Treatment decisions, in contrast, tend to emanate from a complex combination of patient characteristics and prescriber preferences. When real-world data are used to evaluate safety and effectiveness of drugs, the non-randomized treatment assignment, if not properly accounted for, may result in biases, including unmeasured confounding and confounding by indication. These challenges in real-world data analysis and interpretation contribute to hesitancy of the scientific community to trust evidence generated from real-world data, as compared with evidence from randomized clinical trials. Analyses are further complicated by treatments that vary over time, for example if a regimen is changed because of an altered diagnosis or prognosis (e.g., a relapsed cancer case) or due to the approval of new drug treatment options.

We will use the example of multiple myeloma (MM) to demonstrate how pharmacoepidemiologic techniques can be used to study risk of hematologic adverse events during treatment for a cancer recurrence. As a disease that is characterized by repeated relapses and remissions, MM is a strong use case for this example because the real-world comparative safety and effectiveness of MM treatments may differ from efficacy observed in clinical trial populations due to the complex treatment algorithm, which is informed by many patient-level (e.g., comorbidities, treatment history) and provider-level (e.g., practice type) characteristics. Key pharmacoepidemiologic methods in study design (e.g., active comparator, new user study design;[111] alignment of treatment assignment, eligibility specification, and time zero of follow-up[34]) and analysis (e.g., inverse probability of treatment weighting) allow us to make use of real-world data for comparative safety analyses despite the lack of randomization at two treatment decision time points, provided the underlying assumptions hold.

Multiple myeloma is a hematologic cancer that begins in the plasma cells (white blood cells that produce antibodies) and impedes the body's ability to fight infection. Patients with MM are characterized by the proliferation of malignant plasma cells in the bone marrow, proteins in the serum and/or urine, and associated bone and organ damage.[112] With an estimated 34,470 new cases occurring in the United States in 2022, MM accounts for about 1.8% of all cancers and 19% of hematologic cancers.[113, 114] MM is most commonly diagnosed among older adults; the median age at diagnosis is 69 years.[113] The overall 5-year relative survival for MM is 57.9%, with deaths most commonly occurring among MM patients at ages 75 to 84 years.[113]

Most MM patients experience myelosuppression, or a reduction of bone marrow activity, which interferes with hemopoiesis (blood cell development) and results in a decreased production of blood cells (red blood cells, white blood cells, and platelets) (see **Figure 13**). This puts MM patients at an increased risk of hematologic complications, including cytopenias (abnormally low blood cell counts).[115-119] Cytopenias may result from low counts of red blood cells (anemia), white blood cells (leukopenia, neutropenia, lymphocytopenia), or platelets (thrombocytopenia)[120]

Figure 13. Development of blood stem cells into red blood cells, white blood cells, or platelets

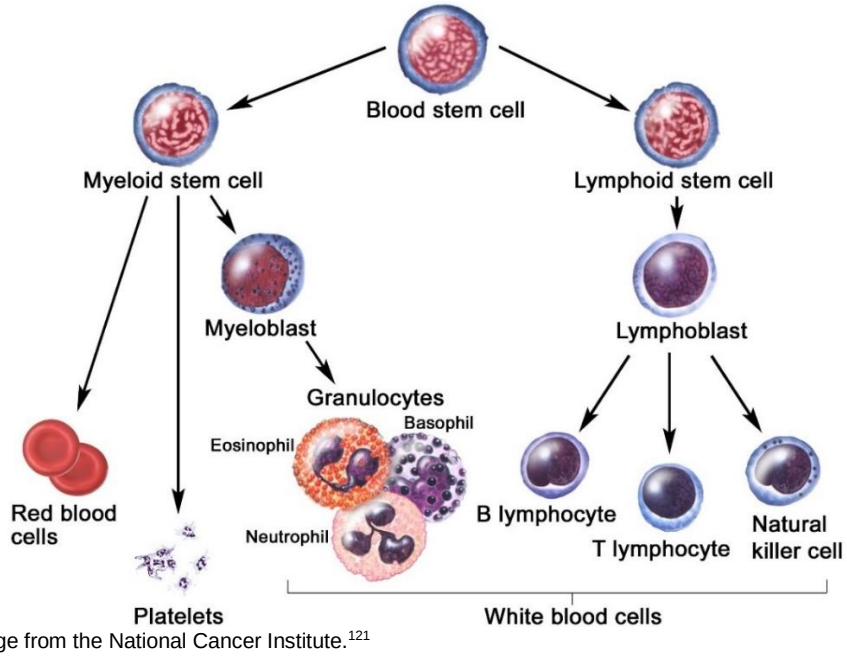


Image from the National Cancer Institute.[121]

Myelosuppression may be exacerbated by MM treatment regimens. There are many available drug treatments for MM, which may be given individually (monotherapy) or in combination with each other (e.g., doublet, triplet, quad, etc.; **Table 12**).[122]

Table 12. Multiple myeloma treatment description by category

Combination	Class groups	Description
Monotherapy	Monoclonal antibody	Daratumumab OR elotuzumab
	PI	Carfilzomib OR bortezomib OR ixazomib
	IMiD	Thalidomide OR lenalidomide OR pomalidomide
	Steroid monotherapy	Dexamethasone OR prednisone
	Targeted inhibitor	Selinexor OR venetoclax
	Other	Any other monotherapy not listed above, including clinical trial drugs
Doublet	Monoclonal antibody + Dex	Daratumumab OR elotuzumab; AND dexamethasone
	PI + Dex	Carfilzomib OR bortezomib OR ixazomib; AND dexamethasone
	IMiD + Dex	Thalidomide OR lenalidomide OR pomalidomide; AND dexamethasone
	Other	Any other doublet not listed above, including clinical trial drugs
Triplet	Monoclonal antibody + PI + IMiD	Daratumumab OR elotuzumab; AND carfilzomib OR bortezomib OR ixazomib; AND thalidomide OR lenalidomide OR pomalidomide
	PI + IMiD + chemotherapy	Carfilzomib OR bortezomib OR ixazomib; AND thalidomide OR lenalidomide OR pomalidomide; AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR vorinostat OR doxorubicin pegylated liposomal
	Monoclonal antibody + PI + Dex	Daratumumab OR elotuzumab; AND carfilzomib OR bortezomib OR ixazomib; AND dexamethasone
	Monoclonal antibody + IMiD + Dex	Daratumumab OR elotuzumab; AND thalidomide OR lenalidomide OR pomalidomide; AND dexamethasone
	PI + IMiD + Dex	Carfilzomib OR bortezomib OR ixazomib; AND thalidomide OR lenalidomide OR pomalidomide; AND dexamethasone
	PI + chemotherapy + Dex	Carfilzomib OR bortezomib OR ixazomib; AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR vorinostat OR doxorubicin pegylated liposomal; AND dexamethasone
	IMiD + chemotherapy + Dex	Thalidomide OR lenalidomide OR pomalidomide; AND bendamustine OR bendamustine HCl OR cisplatin OR cyclophosphamide OR etoposide OR melphalan OR panobinostat OR vincristine OR vincristine sulfate OR vorinostat OR doxorubicin pegylated liposomal; AND dexamethasone
	Other	Any other triplet not listed above, including clinical trial drugs
Quad	Monoclonal antibody + PI + IMiD + Dex	Daratumumab OR elotuzumab; AND carfilzomib OR bortezomib OR ixazomib; AND thalidomide OR lenalidomide OR pomalidomide; AND dexamethasone
	Other	Any other quad not listed above, including clinical trial drugs

Dex: dexamethasone; IMiD: immunomodulatory imide drug; HCl: hydrochloride; PI: proteasome inhibitor
Adapted from Braunlin et al.[122]

The recommended frontline treatment regimens for MM include immunomodulatory drugs (IMiDs; e.g., lenalidomide, pomalidomide, thalidomide), which are received by over 70% of MM patients.[122-124] IMiDs have several mechanisms of anti-cancer action in MM, which are related to both direct cancer cell attack and indirect disruption of the actions of cancer cells in the bone marrow, including starving the cancer cell from nutrients and preventing ongoing inflammation and proliferation of the cancer cells.[125, 126] Cytopenias are generally more commonly associated with regimens containing IMiDs than IMiD-free regimens.[127-129] IMiDs have been linked to the downregulation of transcription factors involved in the development of myeloid cells (type of bone marrow cells) and the differentiation of downstream granulocytes (which give rise to neutrophils), thereby disrupting vital neutrophil processes and resulting in neutropenia (**Figure 13**).[130, 131] The impact of reduction in these transcription factors does not appear to impact lymphoid cells, which give rise to lymphocytes; other mechanisms for IMiD-related lymphocytopenia have not been described in the literature.[132] Similar potential biologic mechanisms have been described for other downstream myeloid cells, erythrocytes (which give rise to red blood cells) and megakaryocytes (which give rise to platelets), which could contribute to IMiD-associated anemia and thrombocytopenia, although these processes are not well understood.[133, 134]

The incidence of grades 3 or 4 cytopenias reported in randomized clinical trials of MM patients involving IMiD treatment arms is displayed in **Table 13**. In general, cytopenias occurred more commonly in IMiD arms than in placebo arms, especially in trial populations of relapsed and refractory MM patients compared with newly diagnosed MM patients. Neutropenia, leukopenia, thrombocytopenia, and anemia are recognized as common adverse reactions (≥20%) of lenalidomide in MM patients, based on data from randomized clinical trials.[135-142] The risk of neutropenia in lenalidomide-treated MM patients has been observed to be as high as 60%, and may vary based on the combination of other drugs in the given treatment regimen.[142, 143]

Similarly, pomalidomide, which is indicated for relapsed and refractory MM patients in combination with dexamethasone, includes a hematology toxicology warning on its label, particularly for the high rates of neutropenia incidence (about 41–62%).[144-148] In contrast, neutropenia does not appear to be a common side effect of thalidomide, affecting less than 10% of MM patients.[149, 150]

Table 13. Incidence of treatment-related grades 3 or 4 cytopenias among multiple myeloma in randomized clinical trials patients involving treatment arms with immunomodulatory drugs

ClinicalTrials.gov Identifier	Treatment Arm	N	Anemia	Leukopenia	Neutropenia	Lymphocytopenia	Thrombocytopenia
Newly Diagnosed							
NCT00033332[149, 151]	Thalidomide + Dex	102	-	6 (6%)	10 (10%)	-	-
	Placebo	102	-	3 (3%)	10 (10%)	-	-
NCT00057564[150, 151]	Thalidomide + Dex	234	-	-	8 (3%)	-	-
	Placebo	232	7 (4%)	-	6 (3%)	-	-
NCT00689936[135, 152]	Lenalidomide	532	97 (18%)	24 (5%)	148 (28%)	30 (6%)	44 (8%)
	IMiD Median		*18%*	*6%*	*10%*	*6%*	*8%*
	Placebo Median		*4%*	*3%*	*7%*	-	-
Relapsed/refractory							
NCT00056160[140]	Lenalidomide + Dex	177	23 (13%)	-	73 (41%)	-	26 (15%)
	Placebo	175	9 (5%)	-	8 (5%)	-	12 (7%)
NCT00424047[139]	Lenalidomide + Dex	176	15 (9%)	-	52 (30%)	-	20 (11%)
	Placebo	175	12 (7%)	-	4 (2%)	-	10 (6%)
NCT01311687[145, 148]	Pomalidomide + Dex	300	99 (33%)	27 (9%)	145 (48%)	-	66 (22%)
	Placebo	150	55 (31%)	5 (3%)	24 (16%)	-	39 (26%)
NCT00833833[147, 148]	Pomalidomide	107	25 (23%)	7 (7%)	51 (48%)	2 (2%)	24 (22%)
	Pomalidomide + Dex	112	24 (21%)	11 (10%)	46 (41%)	8 (7%)	21 (19%)
NCT01053949[144]	Pomalidomide + Dex	84	30 (36%)	-	52 (62%)	-	23 (27%)
NCT01712789[146]	Pomalidomide + Dex	676	223 (33%)	54 (8%)	336 (50%)	-	163 (24%)
	IMiD Median		*28%*	*8%*	*48%*	*2%*	*22%*
	Placebo Median		*7%*	*3%*	*5%*	-	*7%*

Dex: dexamethasone; IMiD: immunomodulatory imide drug
- indicates that trial did not report this outcome

The majority of MM patients eventually relapse and subsequent treatment regimens may or may not include IMiDs.[123] Treatment choice for relapsed MM is affected by many factors, including relapse timing and aggressiveness, treatment history (including whether the patient is refractory to a drug), and performance status.[123] It is unknown how the risk of cytopenias may be impacted by exposure to sequential regimens containing IMiDs, as studies have not necessarily examined the comparative risk of adverse events across multiple lines of therapy. The novel IMiD drug-free regimen developed by Amgen in collaboration with Janssen (carfilzomib, dexamethasone, and daratumumab [KdD]) has demonstrated efficacy for progression-free survival in a recent phase 3 study.[153] It is important to understand whether there is a differential risk of cytopenias in MM patients who do versus do not receive sequential treatment with IMiDs to inform future treatment recommendations for relapsed MM patients. Real-world data provide an opportunity to efficiently evaluate comparative hematologic safety of marketed medication regimens for MM (i.e., as opposed to conducting postmarketing clinical trials, in which treatment randomization may not be ethical given knowledge of how treatments may not be well-tolerated in certain patient groups[123]). Demonstrating that real-world data can be used to address comparative safety questions subject to bias due to complex, non-randomized prescribing patterns is imperative for supporting the real-world data initiative and emphasizing how FDA, providers, and patients may rely on real-world data when comparable clinical trial data are not available.

Methods

Data Source

The data source for this aim was the Flatiron Health enhanced datamart, which consists of longitudinal, de-identified electronic health records (EHR) contained in Amgen's Oncology Services Comprehensive Electronic Records database, generated by Flatiron Health (New York, NY, April 2016). The Flatiron database contains EHR from patients treated at about one

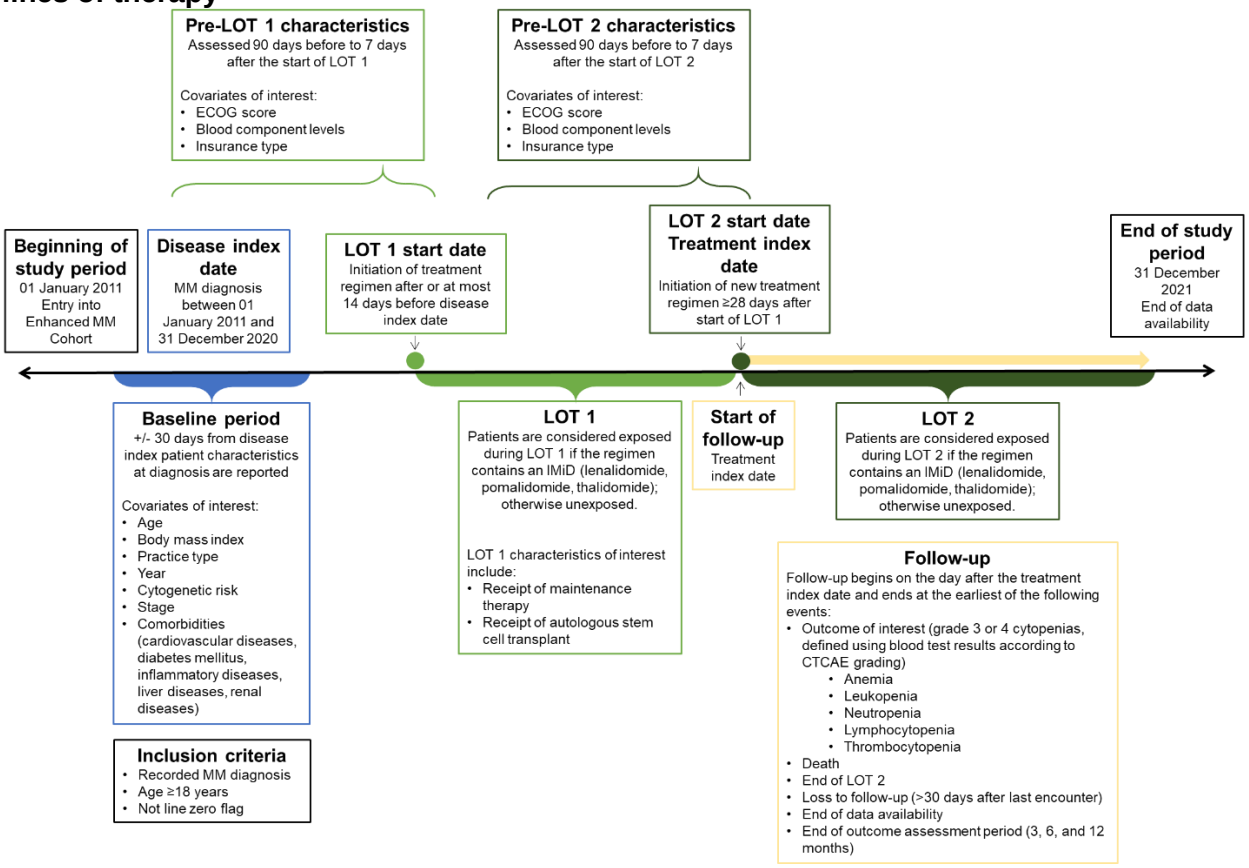
fourth of community-based oncology centers in the United States (about 280 cancer clinics across all 50 states, Puerto Rico, and the District of Columbia) and represents the largest United States real-world oncology data source, making it an ideal data source to examine effectiveness of oncology treatments in a representative dataset. Patients representing all payer types (i.e., Medicare, Medicaid, commercial, self-pay) are included in the database. Information available includes patient demographic characteristics (e.g., state of residence, insurance type, race, ethnicity) and diagnoses, laboratory tests, and treatment administrations, all with dates available. Additionally, treatment setting information is available, including unique practice identifiers and an indicator variable for whether the practice is a community or academic institution. The Flatiron database includes extracted data from structured (e.g., drug administrations, lab values) and unstructured EHR (e.g., physician notes, radiology reports), as well as detailed death information (based on linkage of the EHR with the Social Security Death Index and additional obituary data[154]). For cancer patients who are treated within the Flatiron network, the entire patient chart is available. EHR data are continuously captured so long as the patient is treated at a facility in the Flatiron network (allowing for the possibility of switching facilities within the network); treatment-related data missingness may occur for patients who move to be treated outside of the network. However, given that our study population involves cancer patients who receiving active treatment, most of whom are of advanced age, we do not expect these patients to be moving treatment facilities during the study period. Use of an EHR-derived database as opposed to an insurance claims database for oncology research is advantageous due to the inclusion of detailed staging information and lab test results, which are not typically available in claims data.

Study Population

The study design schema is displayed in **Figure 14**. The cohort included patients ages 18 years or older with a recorded diagnosis of MM (ICD-9 203.0x; ICD-10 C90.0x) who initiated a new

LOT between 01 January 2011 and 31 December 2020 (one year before the end of the latest data availability at the time of this analysis, which allowed for the possibility of a minimum of one year of follow-up data within the database). All patients were required to have at least two LOTs following MM diagnosis. There was no restriction implemented for a maximum amount of time allowed to elapse between the MM diagnosis date and the start of the first LOT, as smoldering myeloma (a precancerous condition that may progress to MM, at which time treatment would be initiated) has ICD codes identical to those of MM and therefore is indistinguishable from MM in the electronic health records database. Patients with a flag indicating receipt of Line Zero were excluded. The Flatiron data uses a Line Zero indicator to indicate patients for whom treatment data may be missing (and therefore LOT 1 may not necessarily correspond to the patient's true first treatment line). The start date of the second LOT was defined as the index date.

Figure 14. Summary of inclusion criteria and baseline variable assessment timing for cohort of multiple myeloma patients in the Flatiron Health database receiving at least two lines of therapy



CTCAE: Common Terminology Criteria for Adverse Events. ECOG: Eastern Cooperative Oncology Group. IMiD: Immunomodulatory imide drug. ISS: International Staging System. LOT: Line of therapy. MM: Multiple myeloma.

Outcome

The outcome of interest was the first recorded occurrence of grade 3 or grade 4 cytopenias, defined using blood test results according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (**Table 14**).[155] We examined the following cytopenias: anemia, leukopenia (including subtypes neutropenia and lymphocytopenia), and thrombocytopenia. The laboratory tests relevant for the measurement of blood levels associated with each cytopenia were defined using Logical Observation Identifiers Names and Codes (LOINC) codes.[156]

Table 14. Cytopenia grading according to the National Cancer Institute's Common Terminology Criteria for Adverse Events

Type	Blood element	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	<LLN to 10 g/dL	8.0 to 10.0 g/dL	<8.0 g/dL	Life-threatening consequences
Leukopenia	Total white blood cells	<LLN to 3,000/μL	2,000 to 3,000/μL	1,000 to 2,000/μL	<1,000/μL
Neutropenia	Neutrophils	<LLN to 1,500/μL	1,000 to 1,500/μL	500 to 1,000/μL	<500/μL
Lymphocytopenia	Lymphocytes	<LLN to 800/μL	500 to 800/μL	200 to 500/μL	<200/μL
Thrombocytopenia	Platelets	<LLN to 75,000/μL	50,000 to 75,000/μL	25,000 to 50,000/μL	<25,000/μL

LLN = lower limit of normal
From the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).[155]

Exposure

The systematic set of drug treatments prescribed to a patient is referred to as a regimen, and each sequential regimen is referred to as a line of therapy (LOT). The Flatiron Health database contains variables indicating the name, number, and start and end dates of each LOT. These variables were defined based on an algorithm developed by a team of clinical experts (oncologists, engineers, biostatisticians) according to medications recorded in the EHR. The start date of the first LOT is defined as the date of the first drug episode given after the MM diagnosis (or at most 14 days before the MM diagnosis, to allow for delayed entry in the EHR, which is common) and after the start of the patient's structured activity (i.e., recording of vital information, medication administration, non-canceled drug order, reported laboratory test/result). The regimen of a given LOT (and, consequently, the name of the LOT) is determined by all eligible drugs given within 28 days of the start of the LOT. De-escalation of a regimen beyond 28 days after the start of the LOT is considered to be the same LOT (e.g., a patient is prescribed the triplet therapy of lenalidomide, bortezomib, and dexamethasone and is subsequently dropped off bortezomib, yet remains on the doublet therapy lenalidomide and dexamethasone). Treatment lines may be advanced due to disease progression or a variety of other reasons (e.g., toxicity, financial burden, patient choice). The administration of a new drug

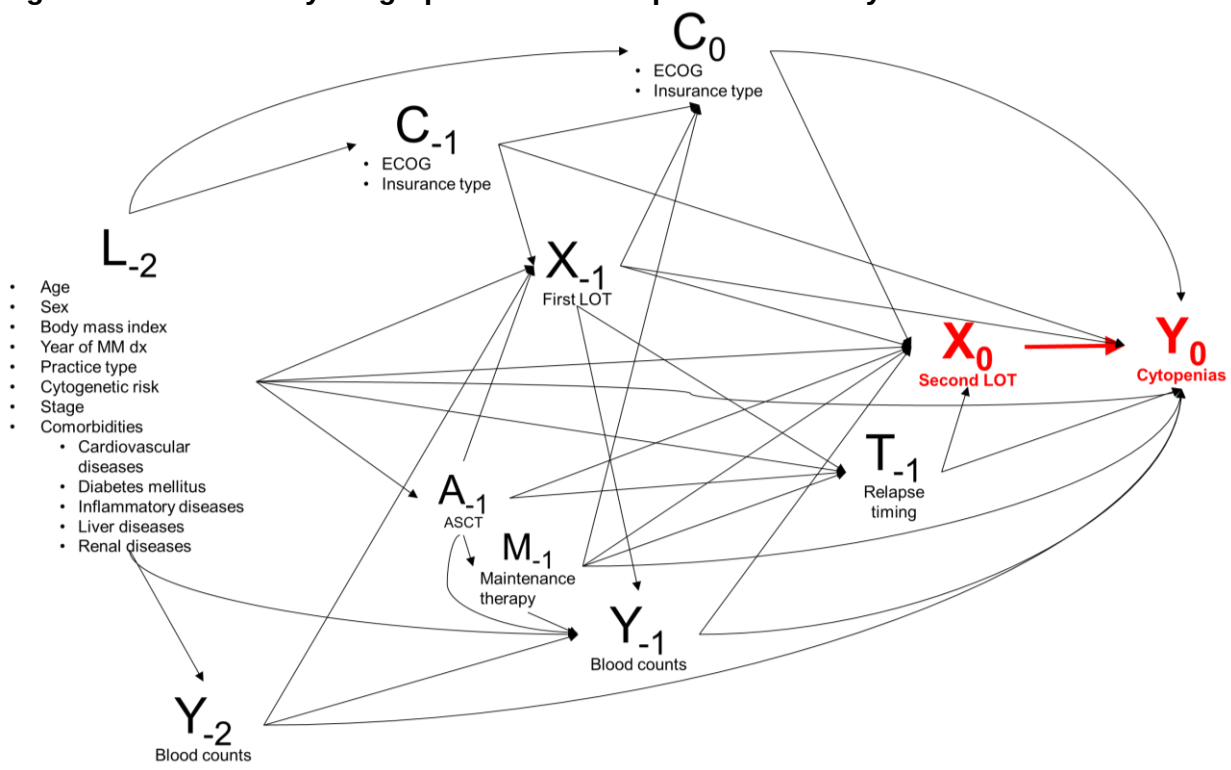
treatment more than 28 days after the LOT start (with certain exceptions made for maintenance therapies and substitutions of biosimilar drugs) is considered to be a new regimen and therefore advances the treatment line. Additionally, if there is a gap of more than 90 days between consecutive episodes of the same regimen, it is assumed that treatment was stopped and then re-started and therefore the LOT is automatically advanced. LOT end dates are defined based on the earliest occurrence of the following: the day before the start of the next LOT, patient death, last structured patient activity, or end of data availability.

Exposure was defined according to the treatment regimens received during the second LOT. An individual was considered exposed if the second LOT line contains IMiDs; an unexposed individual's second LOT contained no IMiDs.

Covariates

See **Figure 15** for a directed acyclic graph (DAG) summarizing the hypothesized relationships between study variables. Treatment decisions at both the first and second lines of therapy are impacted by various fixed, baseline patient characteristics that are also associated with cytopenia risk: patient age,[143, 157, 158] body mass index,[143] MM risk stratification (high- versus standard-risk, based on the International Staging System and cytogenetic abnormalities[159]),[123, 160] and pre-existing comorbidities[123, 157, 161, 162] (renal disease,[143, 158, 163-166] cardiovascular disease,[143, 158, 167-169] liver disease,[143, 169, 170] diabetes mellitus,[143, 165, 171, 172] chronic systemic inflammatory diseases [rheumatoid arthritis, inflammatory bowel disease][171, 173, 174]). Although providers may also consider receipt of other medications for treatment of the comorbidities at the time of MM-related treatment decisions, these other medications are not expected to impact risk of cytopenias and therefore have not been included in this DAG.

Figure 15. Directed acyclic graph of relationship between study variables



X_0: Index exposure at time 0 (second line of therapy)
Y_0: Cytopenias following the second line of therapy
C_0: Time-varying patient and clinic characteristics, assessed at the second line of therapy
X_{-1}: Previous exposure at time -1 (first line of therapy)
T_{-1}: Relapse timing (i.e., the time between start dates of the first and second lines of therapy)
Y_{-1}: Blood component levels following the first line of therapy, assessed before the second line of therapy
C_{-1}: Time-varying patient and clinic characteristics, assessed at the first line of therapy
A_{-1}: Receipt of autologous stem cell transplantation during the first line of therapy
M_{-1}: Receipt of maintenance therapy during the first line of therapy
L_{-2}: Time-fixed patient prognostic characteristics, assessed at the time of multiple myeloma diagnosis
Y_{-2}: Blood component levels before the first line of therapy

Demographic variables such as sex (although a cytopenia risk factor[143]) and race are not expected to be associated with treatment decisions and therefore are not included as confounders in this analysis.[175] Other characteristics of the patient environment, such as year, insurance type, and practice type, may impact the availability of, or provider preference for, certain treatments and are expected to be at least proxies of socioeconomic predictors of cytopenia risk. Given the inclusion of insurance type and practice type as socioeconomic proxies, we did not include geographic location as an additional confounder variable as we do not expect it to be independently associated with cytopenia risk and the literature does not support an association with IMiD prescribing.[175] Time-varying patient characteristics such as

performance status (assessed by the Eastern Cooperative Oncology Group [ECOG] score)[176-179] and blood component levels also affect treatment choice at the first and second LOTs and are expected to impact the risk of developing cytopenias.[158, 180]

Treatment at the first LOT is also driven by patient eligibility for autologous stem cell transplantation (ASCT), which is informed by patient age, performance status, and comorbidities.[123] Transplant eligibility impacts whether a patient receives the ASCT (which would be preceded by induction therapy with the treatment assigned as the first LOT), a process during which the patient receives bone marrow stem cells from a healthy donor, which thereby impacts subsequent blood component levels. The impact of ASCT on cytopenia risk is transient, such that blood counts tend to normalize around 3–6 months post-ASCT. For this reason, we hypothesized ASCT to be directly associated with blood component levels during the first LOT and only indirectly associated with blood component levels during the second LOT.

Treatment choice at the second LOT is also impacted by the history of treatment received at the first LOT, including whether the patient received ASCT and maintenance therapy during the first LOT and the time on treatment.[123, 158, 162, 180] ASCT is typically followed by maintenance therapy (long-term monotherapy or combination therapy [based on patient risk stratification] with bortezomib, lenalidomide, thalidomide, or ixazomib, which aims to sustain treatment responses and delay relapse), which is also expected to impact subsequent blood component levels.[181, 182] Patients who received ASCT generally go on to receive maintenance monotherapy, while the non-transplant population tends to receive doublet or triplet maintenance therapy. Upon disease progression, treatment to which patients have not been refractory are prescribed. Patients are considered refractory to a treatment if disease progression occurs within 60 days of treatment initiation, or if progression occurs while on therapy without at least a minor response to the treatment occurring.[180] The non-transplanted population is therefore more likely to require treatment with a different drug or combination of drugs, given increased likelihood for

refractoriness due to prior exposure to a greater number of drugs, which thereby influences second line treatment. Furthermore, patients that received ASCT tend to stay in remission longer than the non-transplanted population, allowing for them to be eligible to receive newer treatments approved later, which is an important factor in second line treatment decision. Receipt of maintenance therapy, and, further, whether the maintenance regimen contains IMiDs, are expected to impact the blood component levels and the risk of developing cytopenias.[182] The timing of a MM relapse, generally a proxy for previous treatment response and aggressiveness of the relapse, affects the second line treatment decision (both directly in terms of treatment strategy and indirectly in terms of the evolution of new medications) and is expected to impact cytopenia risk due to the degree of underlying myelosuppression.[158, 180, 183] Patient characteristics, first LOT regimen, and receipt of ASCT and maintenance therapy all contribute to how long a patient stays in remission.

Based on this DAG, the minimally sufficient set of variables to control for confounding in the association between X_0 and Y_0 is [L_{-2}, C_0, X_{-1}, Y_{-1}, T_{-1}, M_{-1}]. Age, body mass index, year, cytogenetic risk, year, international staging system (ISS) stage, and pre-existing comorbidities (cardiovascular diseases, diabetes mellitus, inflammatory diseases, liver diseases, and renal diseases) were assessed during the disease baseline period, defined as the 30 days before and after the date of MM diagnosis. Comorbidities were defined according to diagnosis codes from the International Classification of Diseases, using both the Ninth Revision (ICD-9) and Tenth Revision (ICD-10) (**Table 15**).

Table 15. Algorithms for definition of baseline comorbidities

Characteristic	ICD-9 Diagnosis	ICD-10 Diagnosis
Cardiovascular diseases	402.x1, 404.x1, 404.x3, 410, 412, 415, 428, 433.x0, 436, 437.0, 437.1, 438, 440, 441, 442, 443, 444, 447, 451, 452, 453, 557	I11.0, I13.0, I13.2, I21, I22, I25.2, I26, I50, I63.5, I63.8, I63.9, I65, I66, I67.2, I67.8, I69, I70, I71, I72, I73, I74, I77, I79, I80, I81, I82, K55.0, K55.1, K55.9
Diabetes	250.0–250.3, 250.8, 250.9	E10 (not E10.2), E11, E13.2–E13.5, E13.8, E13.9, E14.0, E14.1, E14.6, E14.9
Inflammatory disease	340, 446, 555, 556, 579.0, 696, 710.0, 710.1, 710.3, 714, 720.0	G35, K50, K51, K90.0, L30, L40, L41, L42, L44, M05, M06, M08, M30, M31, M32.10, M33, M34.0, M34.1, M34.9, M45.9
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, 456.0–456.2, 572.2–572.8	B18, K70, K71.3, K71.4, K71.5, K71.7, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, I85.0, I86.4, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Renal disease	403.x1, 404.x2, 404.x3, 582, 583.0–583.7, 585, 586, 588.0, V42.0, V45.1, V56	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18, N19, N25.0, N49.0, N94.0, N99.2

ICD-9: International Classification of Diseases, Ninth Revision. ICD-10: International Classification of Diseases, Tenth Revision.

Body mass index was categorized as not overweight (<25.0), overweight (25.0 to <30), or obese (>30.0). An underweight category (<18.5) was not used due an insufficient number of patients meeting the underweight body mass index. Practice type (community or academic) was recorded once per patient record. Patients with both community and academic practices indicated in their record were included in a separate category. ECOG score (0: Fully active; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2: Ambulatory and capable of all self-care but unable to carry out any work activities; 3: Capable of only limited self-care; 4: Completely disabled. Scores of 3 and 4 were combined in the present analysis due to insufficient number of subjects with score of 4.[176-179]), blood component levels (grade 1–2, grade 3–4, or normal [**Table 14**]), and insurance category were assessed during the treatment baseline period, defined as the 90 days before to the 7 days after the start date of the second LOT. The assessment period for blood component levels was limited at the start date of the first LOT such that pre-first LOT blood tests were not included. For these variables, if more than one value was available during the assessment period, the closest to the start of the second LOT was used. Insurance category is defined by Flatiron. If multiple payer categories were recorded on the date closest to the start of the second LOT, the following hierarchy approach was used to select the payer: Medicaid or other

government program, patient assistance program, workers compensation, self-pay, Medicare, commercial health plan, other payer, then unknown/missing. Finally, treatment history characteristics were assessed between the start and end dates of LOT 1. Separate dichotomous variables were created to indicate whether a patient received treatment with each of the following drug classes during LOT 1: IMiDs, proteasome inhibitors, chemotherapy, and corticosteroids. Receipt of maintenance therapy during LOT 1 was categorized dichotomously. Relapse timing was quantified as the time between the start dates of LOT 1 and LOT 2 and categorized as <6 months, 6–12 months, 12–18 months, 18–24 months, or 24+ months.

Multiple imputation via chained equations was used to impute missing confounder information. Variables with missing information included body mass index, disease characteristics (ISS Stage, ECOG score, and cytogenetic risk at baseline), and baseline blood component levels. The proportions of missingness for each variable are displayed in **Table 18**.

Statistical Analyses

The cumulative risks (within 3, 6, and 12 months of treatment initiation) of each cytopenia were estimated for MM patients exposed and MM patients unexposed to IMiDs during the second LOT. Patients were followed from start date of the second LOT (index date) until the earliest occurrence of cytopenia, death (generalized to the month and year in the Flatiron data, defined here as the 15th day of the month), the end date of the second LOT (which, by definition, censors patients starting a third LOT), loss to follow-up (>30 days after the last clinical encounter), or the end of the study period (31 December 2021). Inverse probability of treatment weighting was used to control for confounding by treatment history at the first LOT and by patient and clinic characteristics as described above. Sub-distribution risk estimators were used to specify death as a competing event; the end of the second LOT, loss to follow-up, and administrative end of the study period were considered to be censoring events.[184] Censoring was assumed to be informative and therefore inverse probability of censoring weights, involving

the same list of confounders described above, were used. The risk differences and risk ratios of each cytopenia (within 3, 6, and 12 months of treatment initiation) were estimated as the contrast of risks for the cumulative risk functions, comparing those exposed to IMiDs to those unexposed to IMiDs during the second LOT.

We explored heterogeneity in the effect of the exposure (IMiDs during LOT 2) on the outcome (cytopenias) according to previous IMiD exposure during LOT 1. This allowed us to consider the risks in four groups, defined according to IMiD exposure across the two lines of therapy (see **Table 16**). Those with exposure pattern $X_{-1} = 1$, $X_0 = 1$ received IMiDs as a part of both the first and second lines of therapy and therefore were considered "sequentially exposed" to IMiDs.

Table 16. Treatment groups according to exposure to immunomodulatory drugs across two lines of therapy

		Effect Modifier LOT 1 (X_{-1})	
		IMiDs (1)	**No IMiDs (0)**
Exposure LOT 2 (X_0)	**IMiDs (1)**	$X_{-1} = 1, X_0 = 1$	$X_{-1} = 0, X_0 = 1$
	No IMiDs (0)	$X_{-1} = 1, X_0 = 0$	$X_{-1} = 0, X_0 = 0$

We examined the risk differences and risk ratios of cytopenia (within 3, 6, and 12 months of LOT 2 initiation) comparing those exposed to IMiDs versus those unexposed to IMiDs during the second LOT stratified by IMiDs status during LOT 1. We evaluated evidence of additive or multiplicative interaction between the first line and second line exposure to IMiDs on the risk of developing cytopenia by comparing these stratified risk differences and risk ratios, respectively. There is homogeneity, or no effect measure modification, on the additive scale when the risk difference contrasting receipt of IMiDs during LOT 2 with no receipt of IMiDs during LOT 2 among those who received IMiDs during LOT 1 is equal to this same risk difference among those who did not receive IMiDs during LOT 1 ($RD_{X_0(X_{-1}=1)} = RD_{X_0(X_{-1}=0)}$). There is homogeneity, or no effect measure modification, on the multiplicative scale when the risk ratio contrasting receipt of IMiDs during LOT 2 with no receipt of IMiDs during LOT 2 among those

who received IMiDs during LOT 1 is equal to this same risk ratio among those who did not receive IMiDs during LOT 1 ($RR_{X_0(X_{-1}=1)} = RR_{X_0(X_{-1}=0)}$).

We also examined the common referent risk differences and risk ratios, comparing the risks among those who received IMiDs as a part of either or both LOTs to those who were never exposed. In particular, for the risk differences: (1) $R_{\mathrm{X}_{-1}=1,\mathrm{X}_0=1} - R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}$, (2) $R_{\mathrm{X}_{-1}=1,\mathrm{X}_0=0} - R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}$, and (3) $R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=1} - R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}$. For the risk ratios: (1) $\frac{R_{\mathrm{X}_{-1}=1,\mathrm{X}_0=1}}{R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}}$, (2) $\frac{R_{\mathrm{X}_{-1}=1,\mathrm{X}_0=0}}{R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}}$, and (3) $\frac{R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=1}}{R_{\mathrm{X}_{-1}=0,\mathrm{X}_0=0}}$.

We then repeated the above analyses, stratified on important risk factors for cytopenias as defined at the time of MM diagnosis: recent history of cytopenias (grade 1–4 cytopenia versus normal blood test result in the 90 days before to the 7 days after the start date of the second LOT), older age (≥75 years versus <75 years) and risk (high- versus normal-risk MM, as characterized by the International Staging System and the presence of cytogenetic abnormalities[159, 185]).

As an exploratory analysis, we examined trends in prescribing of granulocyte colony-stimulating factor (G-CSF; generic name filgrastim) during the follow-up period among the exposure groups described above. Information regarding medications received, with dates, is available in Flatiron. Patients with neutropenia are at an increased risk of developing fever and infection due to low levels of neutrophils, a type of immune cell. G-CSF is used to stimulate neutrophil production, with the intent of preventing infection and neutropenic fevers.[186, 187] We expected prescribing of G-CSF to be specific to neutropenia, and to be a marker of severe neutropenia.

Results

Study Population

A total of 13,421 patients were available in the Flatiron Health enhanced database. Of these patients, 5,573 MM patients received at least two LOTs and were thereby eligible for inclusion (**Figure 16**). 59% (N = 3,296) of patients received IMiDs during LOT 2. The majority (81%) of those receiving IMiDs during LOT 2 were prescribed lenalidomide (**Table 17**). Those receiving, compared to not receiving, IMiDs during LOT 2 were on average younger (mean 66 versus 68 years) and diagnosed in later years (≥2016 54% vs 51%) (**Table 18**).

Figure 16. Summary of attrition of cohort of multiple myeloma patients in the Flatiron Health database receiving at least two lines of therapy

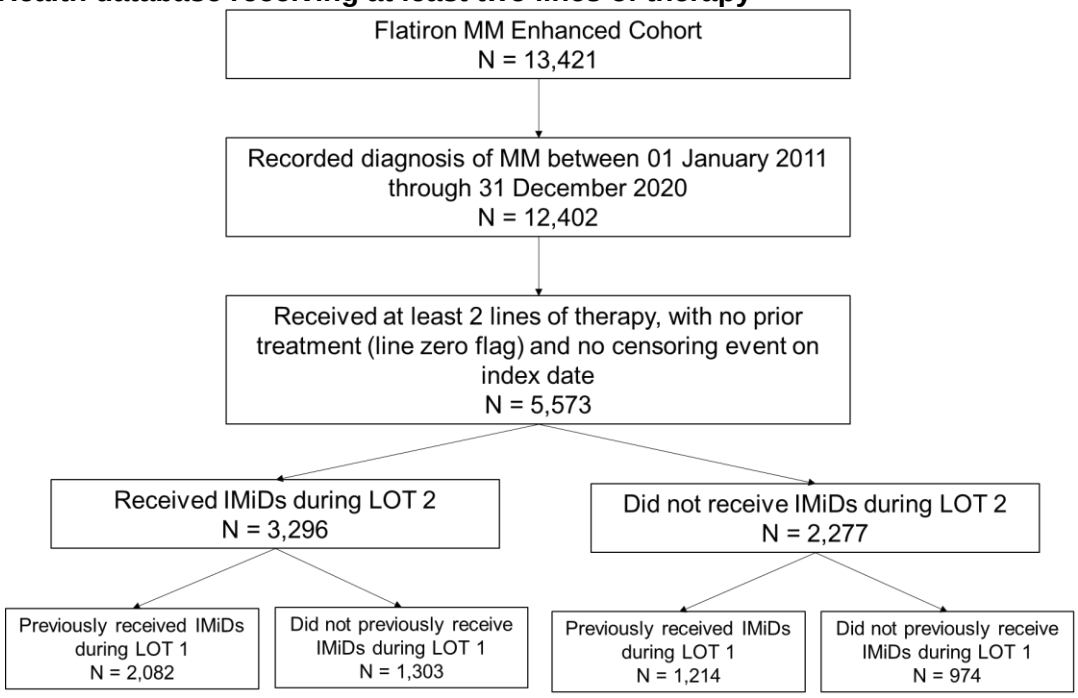


Table 17. Distribution of drugs received among those receiving IMiDs during the second line of therapy

IMiD Drug(s) Received	N (%)
Lenalidomide alone	2,681 (81.3%)
Pomalidomide alone	502 (15.2%)
Thalidomide alone	87 (2.6%)
Lenalidomide and pomalidomide	22 (0.7%)
Lenalidomide and thalidomide	4 (0.1%)

Table 18. Baseline characteristics according to IMiD exposure during the second line of therapy before and after inverse probability of treatment weighting

Characteristic	Before Weighting			After Weighting[1]		
	No L2 IMiD n = 2,277	Yes L2 IMiD n = 3,296	SMD	No L2 IMiD n = 5,569.25	Yes L2 IMiD n = 5,577.21	SMD
Demographics						
Age at diagnosis (years), mean (SD)	67.7 (10.1)	66.2 (10.3)	0.14	66.8 (10.2)	66.8 (10.2)	0.00
Sex						
Female	1,034 (45.4)	1,529 (46.4)	0.02	2,573 (46.2)	2,571 (46.1)	0.00
Male	1,243 (54.6)	1,767 (53.6)		2,996 (53.8)	3,006 (53.9)	
Practice type						
Academic	306 (13.4)	459 (13.9)	0.03	761 (13.7)	762 (13.7)	0.00
Community	1,914 (84.1)	2,770 (84.0)		4,682 (84.1)	4,689 (84.1)	
Both academic and community	57 (2.5)	67 (2.0)		126 (2.3)	126 (2.3)	
Year of diagnosis						
2011	166 (7.3)	227 (6.9)	0.09	393 (7.1)	393 (7.0)	0.01
2012	196 (8.6)	265 (8.0)		464 (8.3)	467 (8.4)	
2013	223 (9.8)	293 (8.9)		507 (9.1)	508 (9.1)	
2014	267 (11.7)	356 (10.8)		627 (11.3)	625 (11.2)	
2015	266 (11.7)	389 (11.8)		637 (11.4)	646 (11.6)	
2016	288 (12.7)	433 (13.1)		728 (13.1)	728 (13.1)	
2017	253 (11.1)	352 (10.7)		608 (10.9)	607 (10.9)	
2018	232 (10.2)	399 (12.1)		634 (11.4)	630 (11.3)	
2019	217 (9.5)	363 (11.0)		583 (10.5)	585 (10.5)	
2020	169 (7.4)	219 (6.6)		389 (7.0)	388 (7.0)	
Insurance payer category						
Commercial health plan	896 (39.4)	1,293 (39.2)	0.05	2,191 (39.3)	2,187 (39.2)	0.01
Medicaid or other government program	157 (6.9)	220 (6.7)		363 (6.5)	371 (6.7)	
Medicare	433 (19.0)	578 (17.5)		1,019 (18.3)	1,018 (18.3)	
Patient assistance program	184 (8.1)	265 (8.0)		455 (8.2)	452 (8.1)	
Other payer	199 (8.7)	297 (9.0)		497 (8.9)	496 (8.9)	
Uninsured or insurance not documented	408 (17.9)	643 (19.5)		1,044 (18.8)	1,052 (18.9)	
Disease Characteristics						
ISS stage at diagnosis						
Stage I	412 (18.1)	683 (20.7)	0.08	1,088 (19.5)	1,092 (19.6)	0.00
Stage II	446 (19.6)	643 (19.5)		1,099 (19.7)	1,102 (19.8)	
Stage III	452 (19.9)	665 (20.2)		1,116 (20.0)	1,115 (20.0)	
Unknown/not documented[2]	967 (42.5)	1,305 (39.6)		2,267 (40.7)	2,269 (40.7)	
Cytogenetic risk at diagnosis						
High risk	258 (11.3)	432 (13.1)	0.05	2,437 (43.8)	2,445 (43.8)	0.00
Standard risk	1,005 (44.1)	1,437 (43.6)		687 (12.3)	689 (12.4)	
Unknown/not documented	1,014 (44.5)	1,427 (43.3)		2,446 (43.9)	2,443 (43.8)	
BMI category at diagnosis						
Not overweight	485 (21.3)	691 (21.0)	0.04	1,164 (20.9)	1,170 (21.0)	0.00
Overweight	637 (28.0)	881 (26.7)		1,521 (27.3)	1,523 (27.3)	
Obese	622 (27.3)	904 (27.4)		1,537 (27.6)	1,532 (27.5)	
Unknown/not documented	533 (23.4)	820 (24.9)		1,347 (24.2)	1,352 (24.2)	
ECOG score, Pre-LOT 2						
0	436 (19.2)	712 (21.6)	0.10	1,157 (20.8)	1,152 (20.7)	0.00
1	671 (29.5)	928 (28.2)		1,589 (28.5)	1,593 (28.6)	
2	267 (11.7)	309 (9.4)		581 (10.4)	581 (10.4)	
3 or 4	65 (2.9)	77 (2.3)		143 (2.6)	143 (2.6)	
Unknown/not documented	838 (36.8)	1,270 (38.5)		2,098 (37.7)	2,108 (37.8)	
Comorbidities						
Cardiovascular diseases	145 (6.4)	184 (5.6)	0.03	328 (5.9)	332 (5.9)	0.00
Diabetes	171 (7.5)	261 (7.9)	0.02	428 (7.7)	430 (7.7)	0.00
Inflammatory diseases	51 (2.2)	59 (1.8)	0.03	111 (2.0)	111 (2.0)	0.00
Liver diseases	28 (1.2)	40 (1.2)	0.00	68 (1.2)	69 (1.2)	0.00
Renal diseases	215 (9.4)	267 (8.1)	0.05	475 (8.5)	475 (8.5)	0.00
LOT 1 Treatment History						
Maintenance therapy	391 (17.2)	607 (18.4)	0.03	1,015 (18.2)	1,006 (18.0)	0.00
IMiD	1,303 (57.2)	2,082 (63.2)	0.12	3,405 (61.1)	3,395 (60.9)	0.01
Proteasome inhibitor	1,532 (67.3)	2,381 (72.2)	0.11	3,914 (70.3)	3,916 (70.2)	0.00
Chemotherapy	361 (15.9)	685 (20.8)	0.13	1,046 (18.8)	1,046 (18.8)	0.00
Corticosteroid	2,005 (88.1)	3,070 (93.1)	0.18	5,069 (91.0)	5,077 (91.0)	0.00
Relapse timing (months)						
<6	751 (33.0)	1,019 (30.9)	0.10	1,765 (31.7)	1,774 (31.8)	0.00
6–12	602 (26.4)	1,008 (30.6)		1,602 (28.8)	1,605 (28.8)	

Characteristic	Before Weighting			After Weighting[1]		
	No L2 IMiD n = 2,277	Yes L2 IMiD n = 3,296	SMD	No L2 IMiD n = 5,569.25	Yes L2 IMiD n = 5,577.21	SMD
12–18	316 (13.9)	472 (14.3)		787 (14.1)	784 (14.1)	
18–24	197 (8.7)	245 (7.4)		444 (8.0)	446 (8.0)	
24+	411 (18.1)	552 (16.8)		971 (17.4)	968 (17.4)	
Cytopenia History						
Hemoglobin level						
Grade 1–2 anemia	1,318 (57.9)	1,807 (54.8)	0.13	3,132 (56.2)	3,133 (56.2)	0.00
Grade 3–4 anemia	98 (4.3)	83 (2.5)		183 (3.3)	186 (3.3)	
Normal	650 (28.6)	1,047 (31.8)		1,695 (30.4)	1,692 (30.3)	
Unknown/not documented	211 (9.3)	359 (10.9)		560 (10.1)	566 (10.2)	
Total white blood cell count						
Grade 1–2 leukopenia	466 (20.5)	716 (21.7)	0.08	1,179 (21.2)	1,181 (21.2)	0.00
Grade 3–4 leukopenia	35 (1.5)	36 (1.1)		74 (1.3)	75 (1.3)	
Normal	1,457 (64.0)	2,016 (61.2)		3,480 (62.5)	3,479 (62.4)	
Unknown/not documented	319 (14.0)	528 (16.0)		835 (15.0)	843 (15.1)	
Absolute neutrophil count						
Grade 1–2 neutropenia	154 (6.8)	224 (6.8)	0.03	394 (7.1)	390 (7.0)	0.01
Grade 3–4 neutropenia	39 (1.7)	57 (1.7)		89 (1.6)	94 (1.7)	
Normal	1,370 (60.2)	1,930 (58.6)		3,301 (59.3)	3,297 (59.1)	
Unknown/not documented	714 (31.4)	1,085 (32.9)		1,786 (32.1)	1,797 (32.2)	
Absolute lymphocyte count						
Grade 1–2 lymphocytopenia	418 (18.4)	612 (18.6)	0.07	1,035 (18.6)	1,031 (18.5)	0.00
Grade 3–4 lymphocytopenia	112 (4.9)	172 (5.2)		280 (5.0)	282 (5.1)	
Normal	1,358 (59.6)	1,867 (56.6)		3,231 (58.0)	3,234 (58.0)	
Unknown/not documented	389 (17.1)	645 (19.6)		1,023 (18.4)	1,030 (18.5)	
Platelet count						
Grade 1–2 thrombocytopenia	388 (17.0)	578 (17.5)	0.13	958 (17.2)	960 (17.2)	0.00
Grade 3–4 thrombocytopenia	65 (2.9)	41 (1.2)		107 (1.9)	109 (2.0)	
Normal	1,420 (62.4)	2,008 (60.9)		3,434 (61.7)	3,437 (61.6)	
Unknown/not documented	404 (17.7)	669 (20.3)		1,070 (19.2)	1,072 (19.2)	

IMiD: Immunomodulatory drug. SD: standard deviation.
[1]Distribution of characteristics after weighting shown here as an example of confounder balance achievable in this cohort for illustrative purposes. In the actual analyses, an iterative process was used to recalculate weights after each iteration of multiple imputation for missing confounder information.
[2]All characteristics with missing data are shown here with a “unknown/not documented” category. All missing values were imputed using multiple imputation.

Patient characteristics were well-balanced after inverse probability of treatment weighting (**Table 18**). Treatment weights according to second LOT IMiD exposure group are summarized in **Table 19**. For both groups, the sum of the weights is approximately equal to the overall sample size (N = 5,573). The absence of very large weights does not support violations or near violations of positivity. Propensity score distributions according to second LOT IMiD exposure group are displayed in **Figure 17**. The probability of receiving an IMiD at the second LOT, given the measured covariates, was similar between those exposed and unexposed as indicated by the largely overlapping propensity score distributions. Neither treatment group had propensity scores of zero or one, which would indicate deterministic exposure assignment based on the measured covariates, thereby supporting the positivity assumption to be met in this cohort. The

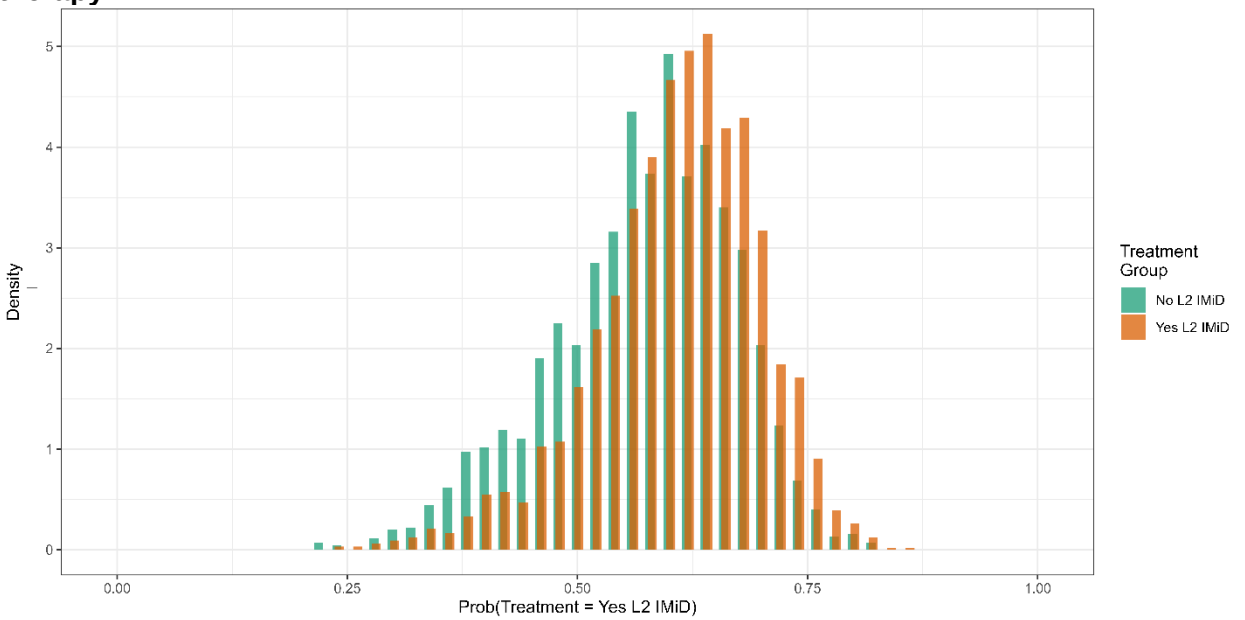
non-overlap in the propensity score distributions was minor, suggesting there to be comparable exposed and unexposed individuals with similar propensity scores.

Table 19. Summary of inverse probability of treatment weights according to IMiD exposure at the second line of therapy

Exposed	Minimum	Percentiles					Maximum	Sum	Mean	Variance
		5th	25th	50th	75th	95th				
No	1.27	1.63	2.05	2.40	2.79	3.47	5.84	5570.95	2.46	0.34
Yes	1.16	1.35	1.49	1.62	1.78	2.26	4.30	5577.08	1.69	0.09

Distribution of inverse probability of treatment weights shown here as an example. In the actual analyses, an iterative process was used to recalculate weights after each iteration of multiple imputation for missing confounder information. These data display the result of a single, randomly chosen imputation for illustrative purposes.

Figure 17. Propensity score distribution according to IMiD exposure at the second line of therapy



Distribution of propensity scores shown here as an example. In the actual analyses, an iterative process was used to recalculate weights after each iteration of multiple imputation for missing confounder information. These data display the result of a single, randomly chosen imputation for illustrative purposes.

Cohort characteristics stratified by IMiD exposure during LOT 1 are also presented in **Table 20**. Most (N = 2,082) were sequentially exposed to IMiDs, with only 974 never exposed. Compared to those never exposed, those sequentially exposed were on average younger (mean 66 versus 69 years), diagnosed at a lower stage (ISS I 24% versus 14%) and in later years (≥2016 62% versus 43%), had a better performance status (ECOG ≤1 55% versus 42%), and had longer time to relapse (≥24 months 20% versus 13%).

Table 20. Baseline characteristics according to IMiD exposure during the first and/or second line of therapy

Characteristic	Yes L1 IMiD		No L1 IMiD		SMD
	Yes L2 IMiD n = 2,082	No L2 IMiD n = 1,303	Yes L2 IMiD n = 1,214	No L2 IMiD n = 974	
Demographics					
Age at diagnosis (years), mean (SD)	65.5 (10.5)	66.7 (10.0)	67.5 (9.9)	68.9 (10.0)	−0.12
Sex					
Female	975 (46.8)	595 (45.7)	554 (45.6)	439 (45.1)	0.02
Male	1,107 (53.2)	708 (54.3)	660 (54.4)	535 (54.9)	
Practice type					
Academic	280 (13.5)	178 (13.7)	179 (14.7)	128 (13.1)	0.03
Community	1,764 (84.7)	1,096 (84.1)	1,006 (82.9)	818 (84.0)	
Both academic and community	38 (1.8)	29 (2.2)	29 (2.4)	28 (2.9)	
Year of diagnosis					
2011	133 (6.4)	95 (7.3)	94 (7.7)	71 (7.3)	0.18
2012	132 (6.3)	97 (7.4)	133 (11.0)	99 (10.2)	
2013	162 (7.8)	109 (8.4)	131 (10.8)	114 (11.7)	
2014	172 (8.3)	122 (9.4)	184 (15.2)	145 (14.9)	
2015	203 (9.8)	136 (10.4)	186 (15.3)	130 (13.4)	
2016	297 (14.3)	162 (12.4)	136 (11.2)	126 (12.9)	
2017	237 (11.4)	174 (13.4)	115 (9.5)	79 (8.1)	
2018	301 (14.5)	132 (10.1)	98 (8.1)	100 (10.3)	
2019	289 (13.9)	160 (12.3)	74 (6.1)	57 (5.9)	
2020	156 (7.5)	116 (8.9)	63 (5.2)	53 (5.4)	
Insurance payer category					
Commercial health plan	872 (41.9)	538 (41.3)	421 (34.7)	358 (36.8)	0.08
Medicaid or other government program	133 (6.4)	77 (5.9)	87 (7.2)	80 (8.2)	
Medicare	342 (16.4)	243 (18.7)	236 (19.4)	190 (19.5)	
Patient assistance program	175 (8.4)	123 (9.4)	90 (7.4)	61 (6.3)	
Other payer	182 (8.7)	106 (8.1)	115 (9.5)	93 (9.6)	
Uninsured or insurance not documented	378 (18.2)	216 (16.6)	265 (21.8)	192 (19.7)	
Disease Characteristics					
ISS stage at diagnosis					
Stage I	491 (23.6)	273 (21.0)	192 (15.8)	139 (14.3)	0.08
Stage II	434 (20.9)	304 (23.3)	209 (17.2)	142 (14.6)	
Stage III	398 (19.1)	235 (18.0)	267 (22.0)	217 (22.3)	
Unknown/not documented[1]	759 (36.5)	491 (37.7)	546 (45.0)	476 (48.9)	
Cytogenetic risk at diagnosis					
High risk	286 (13.7)	156 (12.0)	146 (12.0)	102 (10.5)	0.05
Standard risk	922 (44.3)	598 (45.9)	515 (42.4)	407 (41.8)	
Unknown/not documented	874 (42.0)	549 (42.1)	553 (45.6)	465 (47.7)	
BMI category at diagnosis					
Not overweight	427 (20.5)	272 (20.9)	264 (21.8)	213 (21.9)	0.04
Overweight	566 (27.2)	358 (27.5)	315 (26.0)	279 (28.6)	
Obese	555 (26.7)	363 (27.9)	349 (28.8)	259 (26.6)	
Unknown/not documented	534 (25.7)	310 (23.8)	286 (23.6)	223 (22.9)	
ECOG score, Pre-LOT 2					
0	506 (24.3)	290 (22.3)	206 (17.0)	146 (15.0)	0.10
1	636 (30.6)	407 (31.2)	292 (24.1)	264 (27.1)	
2	181 (8.7)	148 (11.4)	128 (10.5)	119 (12.2)	
3 or 4	51 (2.5)	34 (2.6)	26 (2.1)	31 (3.2)	
Unknown/not documented	708 (34.0)	424 (32.5)	562 (46.3)	414 (42.5)	
Comorbidities					
Cardiovascular diseases	101 (4.9)	70 (5.4)	83 (6.8)	75 (7.7)	0.02
Diabetes	147 (7.1)	94 (7.2)	114 (9.4)	77 (7.9)	0.01
Inflammatory diseases	30 (1.4)	28 (2.2)	29 (2.4)	23 (2.4)	0.05
Liver diseases	26 (1.3)	17 (1.3)	14 (1.2)	11 (1.1)	0.00
Renal diseases	128 (6.2)	80 (6.1)	139 (11.5)	135 (13.9)	0.00
LOT 1 Treatment History					
Maintenance therapy	519 (24.9)	315 (24.2)	88 (7.3)	76 (7.8)	0.02
Proteasome inhibitor	1,464 (70.3)	872 (66.9)	917 (75.5)	660 (67.8)	0.07
Chemotherapy	128 (6.2)	74 (5.7)	557 (45.9)	287 (29.5)	0.02
Corticosteroid	1,998 (96.0)	1,250 (95.9)	1,072 (88.3)	755 (77.5)	0.00
Relapse timing (months)					
<6	499 (24.0)	326 (25.0)	520 (42.8)	425 (43.6)	0.09
6–12	649 (31.2)	360 (27.6)	359 (29.6)	242 (24.9)	

Characteristic	Yes L1 IMiD		No L1 IMiD		SMD
	Yes L2 IMiD n = 2,082	No L2 IMiD n = 1,303	Yes L2 IMiD n = 1,214	No L2 IMiD n = 974	
12–18	336 (16.1)	206 (15.8)	136 (11.2)	110 (11.3)	
18–24	178 (8.6)	124 (9.5)	67 (5.5)	73 (7.5)	
24+	420 (20.2)	287 (22.0)	132 (10.9)	124 (12.7)	
Cytopenia History					
Hemoglobin level					
Grade 1–2 anemia	1,090 (52.4)	728 (55.9)	717 (59.1)	590 (60.6)	0.13
Grade 3–4 anemia	51 (2.5)	52 (4.0)	32 (2.6)	46 (4.7)	
Normal	724 (34.8)	402 (30.9)	323 (26.6)	248 (25.5)	
Unknown/not documented	217 (10.4)	121 (9.3)	142 (11.7)	90 (9.2)	
Total white blood cell count					
Grade 1–2 leukopenia	532 (25.6)	306 (23.5)	184 (15.2)	160 (16.4)	0.12
Grade 3–4 leukopenia	23 (1.1)	27 (2.1)	13 (1.1)	8 (0.8)	
Normal	1,191 (57.2)	790 (60.6)	825 (68.0)	667 (68.5)	
Unknown/not documented	336 (16.1)	180 (13.8)	192 (15.8)	139 (14.3)	
Absolute neutrophil count					
Grade 1–2 neutropenia	179 (8.6)	109 (8.4)	45 (3.7)	45 (4.6)	0.04
Grade 3–4 neutropenia	50 (2.4)	30 (2.3)	7 (0.6)	9 (0.9)	
Normal	1,209 (58.1)	782 (60.0)	721 (59.4)	588 (60.4)	
Unknown/not documented	644 (30.9)	382 (29.3)	441 (36.3)	332 (34.1)	
Absolute lymphocyte count					
Grade 1–2 lymphocytopenia	398 (19.1)	241 (18.5)	214 (17.6)	177 (18.2)	0.07
Grade 3–4 lymphocytopenia	98 (4.7)	53 (4.1)	74 (6.1)	59 (6.1)	
Normal	1,189 (57.1)	784 (60.2)	678 (55.9)	574 (58.9)	
Unknown/not documented	397 (19.1)	225 (17.3)	248 (20.4)	164 (16.8)	
Platelet count					
Grade 1–2 thrombocytopenia	382 (18.4)	229 (17.6)	196 (16.1)	159 (16.3)	0.16
Grade 3–4 thrombocytopenia	27 (1.3)	44 (3.4)	14 (1.2)	21 (2.2)	
Normal	1,231 (59.1)	795 (61.0)	777 (64.0)	625 (64.2)	
Unknown/not documented	442 (21.2)	235 (18.0)	227 (18.7)	169 (17.4)	

IMiD: Immunomodulatory drug. SD: standard deviation.
[1]All characteristics with missing data are shown here with a “unknown/not documented” category. All missing values were imputed using multiple imputation.

Overall Treatment Effect

The overall treatment effect for the associations between IMiD exposure during the second LOT and risks of severe cytopenias are displayed in **Figure 18** and **Table 21**. The risks of neutropenia and leukopenia were substantially higher at 6 and 12 months, although not at 3 months, among those exposed versus unexposed to IMiDs at LOT 2. For the severe neutropenia outcome, patients were followed for an average of 388 days (419 days for those exposed and 344 days for those unexposed). The 3-, 6-, and 12-month risks of neutropenia among those treated with, versus without, IMiDs at LOT 2, respectively, were 10.8% versus 8.7%, 15.7% versus 10.6%, and 20.9% versus 13.3% (**Figure 18A**). For the severe leukopenia outcome, patients were followed for an average of 408 days (448 days for those exposed and 350 days for those unexposed). The 3-, 6-, and 12-month risks of leukopenia among those

treated with, versus without, IMiDs at LOT 2, respectively, were 10.3% versus 10.1%, 13.8% versus 11.6%, and 17.3% versus 13.0% (**Figure 18B**).

In contrast, the 3-, 6-, and 12-month risks of lymphocytopenia, anemia, and thrombocytopenia were similar among those treated with, versus without, IMiDs at LOT 2. For the severe lymphocytopenia outcome, patients were followed for an average of 345 days (385 days for those exposed and 285 days for those unexposed). The 3-, 6-, and 12-month risks of lymphocytopenia among those treated with, versus without, IMiDs at LOT 2, respectively, were 21.0% versus 23.0%, 25.6% versus 27.2%, and 29.7% versus 31.2% (**Figure 18C**). For the severe anemia outcome, patients were followed for an average of 419 days (468 days for those exposed and 349 days for those unexposed). The 3-, 6-, and 12-month risks of anemia among those treated with, versus without, IMiDs at LOT 2, respectively, were 10.1% versus 11.5%, 13.2% versus 13.7%, and 16.1% versus 16.4% (**Figure 18D**). For the severe thrombocytopenia outcome, patients were followed for an average of 424 days (473 days for those exposed and 352 days for those unexposed). The 3-, 6-, and 12-month risks of thrombocytopenia among those treated with, versus without, IMiDs at LOT 2, respectively, were 7.4% versus 10.7%, 10.8% versus 12.3%, and 13.8% versus 13.7% (**Figure 18E**).

Figure 18. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy

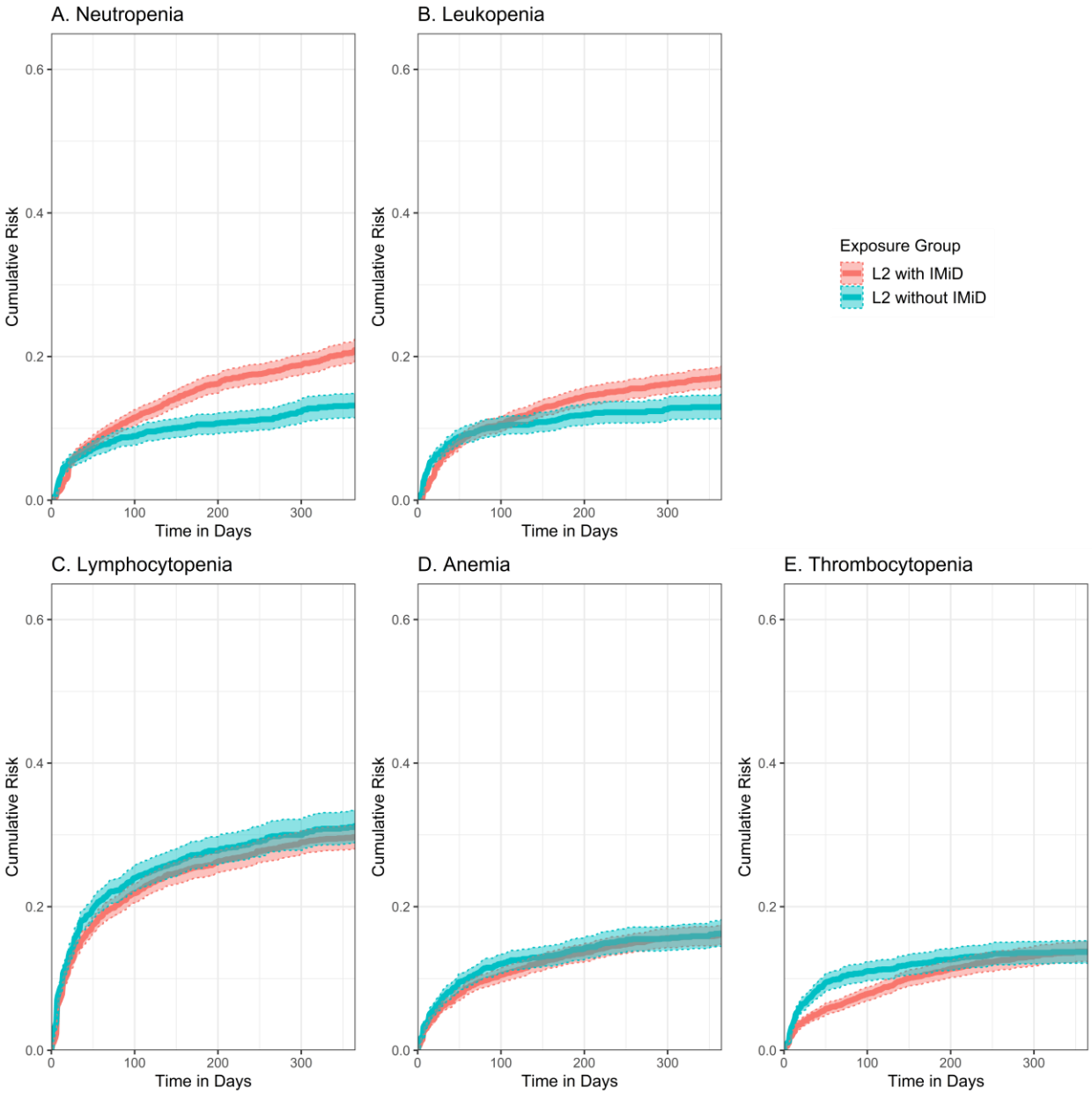


Table 21. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs

	Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Not Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Risk Ratio (95% CI)
Anemia				
3 months	10.1 (9.1, 11.0)	11.5 (10.2, 12.8)	-1.4 (-3.0, 0.1)	0.9 (0.8, 1.0)
6 months	13.2 (12.0, 14.4)	13.7 (12.2, 15.2)	-0.5 (-2.3, 1.2)	1.0 (0.8, 1.1)
12 months	16.1 (14.8, 17.5)	16.4 (14.6, 18.3)	-0.3 (-2.4, 1.8)	1.0 (0.9, 1.1)
Leukopenia				
3 months	10.3 (9.2, 11.4)	10.1 (8.8, 11.3)	0.2 (-1.4, 1.8)	1.0 (0.9, 1.2)
6 months	13.8 (12.6, 15.0)	11.6 (10.2, 13.0)	2.2 (0.4, 4.0)	1.2 (1.0, 1.4)
12 months	17.3 (15.8, 18.7)	13.0 (11.4, 14.7)	4.2 (2.0, 6.4)	1.3 (1.1, 1.5)
Neutropenia				
3 months	10.8 (9.8, 11.9)	8.7 (7.5, 10.0)	2.1 (0.4, 3.7)	1.2 (1.0, 1.5)
6 months	15.7 (14.3, 17.0)	10.6 (9.2, 12.0)	5.1 (3.1, 7.0)	1.5 (1.3, 1.7)
12 months	20.9 (19.4, 22.5)	13.3 (11.6, 15.1)	7.6 (5.4, 9.8)	1.6 (1.3, 1.8)
Lymphocytopenia				
3 months	21.0 (19.6, 22.3)	23.0 (21.3, 24.7)	-2.0 (-4.2, 0.1)	0.9 (0.8, 1.0)
6 months	25.6 (24.0, 27.1)	27.2 (25.3, 29.2)	-1.7 (-4.2, 0.8)	0.9 (0.9, 1.0)
12 months	29.7 (28.1, 31.3)	31.2 (29.0, 33.5)	-1.5 (-4.4, 1.3)	1.0 (0.9, 1.0)
Thrombocytopenia				
3 months	7.4 (6.5, 8.3)	10.7 (9.4, 12.0)	-3.3 (-4.8, -1.9)	0.7 (0.6, 0.8)
6 months	10.8 (9.6, 12.0)	12.3 (10.9, 13.8)	-1.5 (-3.3, 0.2)	0.9 (0.7, 1.0)
12 months	13.8 (12.4, 15.2)	13.7 (12.1, 15.3)	0.1 (-1.9, 2.0)	1.0 (0.9, 1.2)

Treatment Effect Stratified by Prior Exposure

The treatment effect for the associations between IMiD exposure during the second LOT and risks of severe cytopenias, stratified by prior IMiD exposure during the first LOT, are displayed in **Figure 19** and **Table 22**. There was no evidence of additive or multiplicative interaction between the first and second LOTs on the risks of any of the severe cytopenias under study based on the stratified RDs and RRs at 3, 6, and 12 months. For neutropenia and leukopenia, using the common referent approach revealed a trend in which the 3-, 6-, and 12-month risks were highest for those sequentially exposed and lowest for those never exposed (**Figure 19A–B**). Interestingly, for both cytopenias, the risk among those with only past exposure during LOT 1 was higher than that of those only currently exposed during LOT 2 at 3 and 6 months, yet these risks switched at 12 months. Stratification on prior IMiD exposure did not meaningfully change the risks of lymphocytopenia or anemia (**Figure 19C–D**). Finally, for thrombocytopenia, those sequentially, versus never, exposed appeared to have an increased risk at 12 months (13.0% versus 10.8%), but not at 3 (7.4% versus 7.5%) and 6 months (10.5% versus 9.2%).

The risk among those with only past exposure, however, was the highest across the entirety of follow-up (**Figure 19E**).

Figure 19. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by first line of therapy exposure

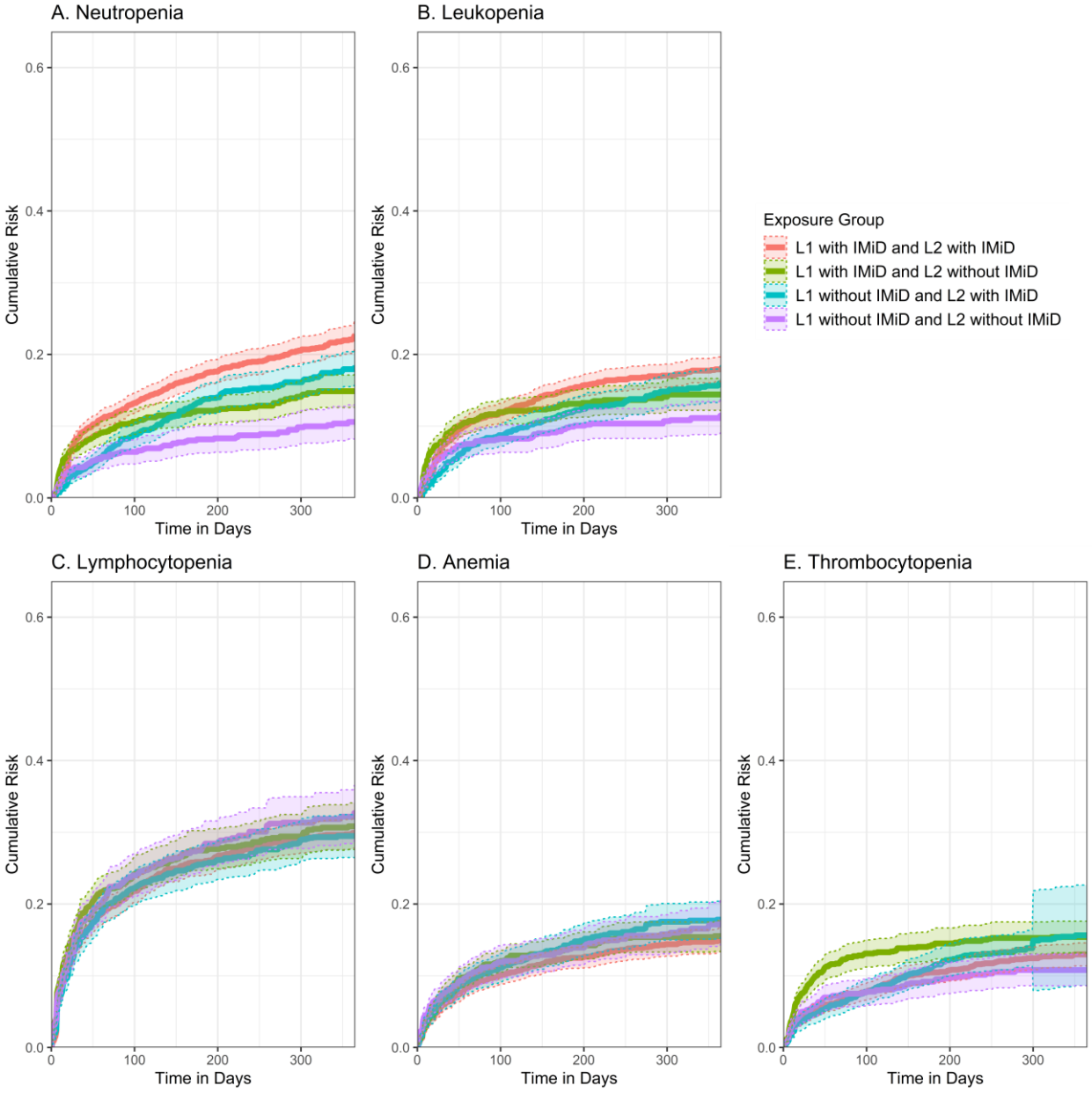


Table 22. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by first line of therapy exposure

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
Anemia				
3 months				
Risk /100 (95% CI)	9.7 (8.4, 10.9)	11.6 (10.1, 13.1)	10.7 (8.8, 12.6)	11.2 (9.0, 13.5)
Stratified RD /100 (95% CI)	-1.9 (-3.8, -0.1)	Ref	-0.5 (-3.4, 2.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	-1.6 (-4.1, 1.0)	0.4 (-2.3, 3.0)	-0.5 (-3.4, 2.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	12.4 (11.0, 13.9)	13.8 (12.0, 15.6)	14.2 (12.0, 16.4)	13.6 (11.2, 16.0)
Stratified RD /100 (95% CI)	-1.3 (-3.5, 0.8)	Ref	0.6 (-2.5, 3.8)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	1.1 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	-1.2 (-3.9, 1.6)	0.2 (-2.7, 3.1)	0.6 (-2.5, 3.8)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	Ref
12 months				
Risk /100 (95% CI)	15.1 (13.3, 16.8)	15.5 (13.4, 17.7)	17.8 (15.2, 20.4)	17.7 (14.5, 20.9)
Stratified RD /100 (95% CI)	-0.5 (-2.9, 2.0)	Ref	0.2 (-4.0, 4.3)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	1.0 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	-2.6 (-6.1, 0.9)	-2.1 (-5.9, 1.6)	0.2 (-4.0, 4.3)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	Ref
Leukopenia				
3 months				
Risk /100 (95% CI)	11.5 (10.2, 12.9)	11.7 (9.9, 13.4)	8.4 (6.9, 9.8)	8.0 (6.1, 9.9)
Stratified RD /100 (95% CI)	-0.1 (-2.2, 2.0)	Ref	0.3 (-2.0, 2.7)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.7, 1.4)	Ref
Common Ref RD /100 (95% CI)	3.5 (1.3, 5.8)	3.7 (1.0, 6.3)	0.3 (-2.0, 2.7)	Ref
Common Ref RR (95% CI)	1.5 (1.1, 1.9)	1.5 (1.0, 1.9)	1.1 (0.7, 1.4)	Ref
6 months				
Risk /100 (95% CI)	15.0 (13.6, 16.5)	13.0 (11.1, 14.9)	11.8 (10.0, 13.7)	9.8 (7.7, 11.9)
Stratified RD /100 (95% CI)	2.0 (-0.3, 4.4)	Ref	2.0 (-0.7, 4.7)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.4)	Ref	1.2 (0.9, 1.5)	Ref
Common Ref RD /100 (95% CI)	5.2 (2.7, 7.7)	3.2 (0.4, 6.0)	2.0 (-0.7, 4.7)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (0.9, 1.5)	Ref
12 months				
Risk /100 (95% CI)	17.9 (16.2, 19.6)	14.4 (12.2, 16.6)	16.1 (13.7, 18.6)	11.5 (9.1, 13.9)
Stratified RD /100 (95% CI)	3.5 (0.7, 6.3)	Ref	4.7 (1.2, 8.2)	Ref
Stratified RR (95% CI)	1.3 (1.0, 1.5)	Ref	1.4 (1.0, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.5 (3.6, 9.3)	3.0 (-0.2, 6.1)	4.7 (1.2, 8.2)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.6)	1.4 (1.0, 1.8)	Ref
Neutropenia				
3 months				
Risk /100 (95% CI)	12.5 (11.1, 13.8)	10.3 (8.6, 12.0)	8.2 (6.6, 9.9)	6.4 (4.7, 8.1)
Stratified RD /100 (95% CI)	2.2 (-0.1, 4.4)	Ref	1.8 (-0.6, 4.2)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.5)	Ref	1.3 (0.9, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.1 (4.0, 8.1)	3.9 (1.4, 6.3)	1.8 (-0.6, 4.2)	Ref
Common Ref RR (95% CI)	2.0 (1.4, 2.5)	1.6 (1.1, 2.2)	1.3 (0.9, 1.8)	Ref
6 months				
Risk /100 (95% CI)	17.0 (15.4, 18.6)	12.1 (10.3, 14.0)	13.6 (11.4, 15.8)	8.2 (6.2, 10.1)
Stratified RD /100 (95% CI)	4.9 (2.4, 7.4)	Ref	5.4 (2.4, 8.4)	Ref
Stratified RR (95% CI)	1.4 (1.2, 1.7)	Ref	1.7 (1.2, 2.2)	Ref
Common Ref RD /100 (95% CI)	8.8 (6.4, 11.3)	4.0 (1.4, 6.5)	5.4 (2.4, 8.4)	Ref
Common Ref RR (95% CI)	2.1 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.2, 2.2)	Ref
12 months				
Risk /100 (95% CI)	22.6 (20.7, 24.6)	15.1 (12.7, 17.5)	18.1 (15.7, 20.5)	10.6 (8.2, 13.0)
Stratified RD /100 (95% CI)	7.5 (4.5, 10.5)	Ref	7.5 (4.3, 10.7)	Ref
Stratified RR (95% CI)	1.5 (1.2, 1.8)	Ref	1.7 (1.3, 2.2)	Ref
Common Ref RD /100 (95% CI)	12.1 (9.0, 15.1)	4.5 (1.2, 7.9)	7.5 (4.3, 10.7)	Ref
Common Ref RR (95% CI)	2.2 (1.6, 2.7)	1.4 (1.1, 1.8)	1.7 (1.3, 2.2)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Lymphocytopenia				
3 months				
Risk /100 (95% CI)	20.8 (19.2, 22.5)	23.0 (20.7, 25.3)	21.4 (19.0, 23.8)	23.4 (20.5, 26.3)
Stratified RD /100 (95% CI)	-2.1 (-5.1, 0.8)	Ref	-2.0 (-5.7, 1.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.0)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	-2.6 (-6.0, 0.8)	-0.4 (-4.3, 3.4)	-2.0 (-5.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	Ref
6 months				
Risk /100 (95% CI)	25.9 (23.9, 27.8)	27.5 (24.7, 30.2)	25.5 (22.8, 28.2)	27.5 (24.3, 30.6)
Stratified RD /100 (95% CI)	-1.6 (-5.2, 1.9)	Ref	-2.0 (-5.9, 1.9)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	-1.6 (-5.3, 2.1)	0.0 (-4.4, 4.4)	-2.0 (-5.9, 1.9)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	Ref
12 months				
Risk /100 (95% CI)	29.9 (27.8, 32.0)	30.8 (27.6, 34.1)	29.5 (26.5, 32.5)	32.7 (28.8, 36.5)
Stratified RD /100 (95% CI)	-0.9 (-5.0, 3.1)	Ref	-3.2 (-8.0, 1.6)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.8, 1.0)	Ref
Common Ref RD /100 (95% CI)	-2.8 (-7.2, 1.7)	-1.8 (-7.0, 3.3)	-3.2 (-8.0, 1.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	Ref
Thrombocytopenia				
3 months				
Risk /100 (95% CI)	7.4 (6.3, 8.4)	12.8 (11.0, 14.7)	7.4 (5.7, 9.0)	7.5 (5.7, 9.3)
Stratified RD /100 (95% CI)	-5.5 (-7.5, -3.4)	Ref	-0.1 (-2.5, 2.2)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.7)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	-0.1 (-2.2, 2.0)	5.3 (2.6, 8.0)	-0.1 (-2.5, 2.2)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.3)	1.7 (1.2, 2.2)	1.0 (0.7, 1.3)	Ref
6 months				
Risk /100 (95% CI)	10.5 (9.0, 11.9)	14.3 (12.2, 16.4)	11.4 (9.2, 13.6)	9.2 (7.1, 11.3)
Stratified RD /100 (95% CI)	-3.8 (-6.3, -1.4)	Ref	2.2 (-0.8, 5.1)	Ref
Stratified RR (95% CI)	0.7 (0.6, 0.9)	Ref	1.3 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.3 (-1.3, 3.9)	5.1 (2.0, 8.2)	2.2 (-0.8, 5.1)	Ref
Common Ref RR (95% CI)	1.2 (0.8, 1.5)	1.6 (1.1, 2.0)	1.3 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	13.0 (11.4, 14.6)	15.4 (13.2, 17.6)	15.6 (8.6, 22.6)	10.8 (8.6, 13.0)
Stratified RD /100 (95% CI)	-2.4 (-5.0, 0.2)	Ref	4.8 (-2.4, 12.0)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.5 (0.8, 2.1)	Ref
Common Ref RD /100 (95% CI)	2.2 (-0.5, 4.9)	4.6 (1.4, 7.8)	4.8 (-2.4, 12.0)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.4 (1.1, 1.8)	1.5 (0.8, 2.1)	Ref

Treatment Effect according to Cytopenia History

The associations between IMiD exposure during the second LOT and risks of severe cytopenias, stratified by history of each given cytopenia, are displayed in **Figure 20** and **Table 23**. The risks of all severe cytopenias following second LOT initiation were substantially lower among those with no recent cytopenia history. There was no evidence of additive or multiplicative interaction between second LOT IMiD exposure and cytopenia history on the risks of any of the severe cytopenias based on the stratified RDs and RRs at 3, 6, and 12 months.

Figure 20. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by recent history of the given cytopenia

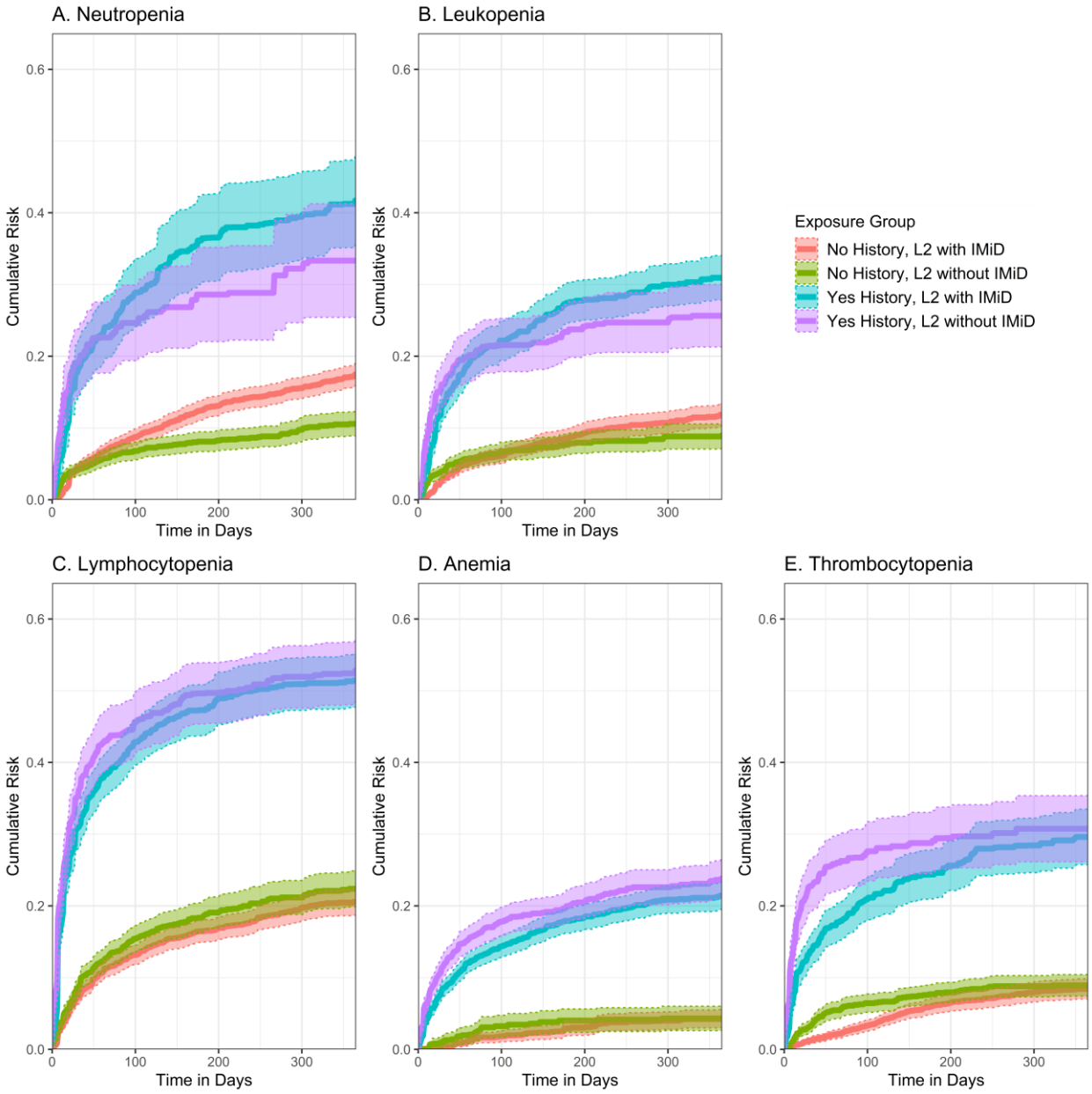


Table 23. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by recent history of the given cytopenia

	Exposed to IMiDs during LOT 2 ($X_0 = 1$) Risk / 100 (95% CI)	Not Exposed to IMiDs during LOT 2 ($X_0 = 0$) Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Risk Ratio (95% CI)
Cytopenia History				
Anemia				
3 months	13.9 (12.4, 15.4)	17.0 (15.1, 19.0)	−3.2 (−5.7, −0.7)	0.8 (0.7, 0.9)
6 months	17.9 (16.2, 19.7)	20.0 (17.7, 22.2)	−2.1 (−4.9, 0.8)	0.9 (0.8, 1.0)
12 months	21.4 (19.5, 23.3)	23.8 (21.1, 26.5)	−2.4 (−5.6, 0.9)	0.9 (0.8, 1.0)
Leukopenia				
3 months	21.4 (18.7, 24.2)	21.4 (17.7, 25.1)	0.1 (−4.7, 4.8)	1.0 (0.8, 1.2)
6 months	27.4 (24.6, 30.2)	23.4 (19.5, 27.2)	4.0 (−0.8, 8.9)	1.2 (0.9, 1.4)
12 months	30.9 (27.8, 34.0)	25.6 (21.3, 30.0)	5.3 (0.1, 10.5)	1.2 (1.0, 1.5)
Neutropenia				
3 months	27.5 (23.0, 32.1)	24.6 (19.4, 29.9)	2.9 (−4.3, 10.0)	1.1 (0.8, 1.5)
6 months	36.4 (30.4, 42.5)	28.6 (22.0, 35.2)	7.8 (−1.5, 17.2)	1.3 (0.9, 1.7)
12 months	41.7 (35.5, 47.9)	33.3 (25.4, 41.3)	8.4 (−1.6, 18.4)	1.3 (0.9, 1.6)
Lymphocytopenia				
3 months	41.1 (37.9, 44.2)	44.4 (40.2, 48.5)	−3.3 (−9.0, 2.4)	0.9 (0.8, 1.1)
6 months	47.3 (43.7, 50.8)	49.6 (45.4, 53.9)	−2.3 (−8.3, 3.6)	1.0 (0.8, 1.1)
12 months	51.4 (47.7, 55.2)	52.8 (48.4, 57.2)	−1.4 (−7.5, 4.7)	1.0 (0.9, 1.1)
Thrombocytopenia				
3 months	20.3 (17.3, 23.2)	26.7 (22.8, 30.7)	−6.5 (−11.3, −1.7)	0.8 (0.6, 0.9)
6 months	24.4 (21.0, 27.8)	29.1 (24.8, 33.3)	−4.7 (−10.0, 0.6)	0.8 (0.7, 1.0)
12 months	29.6 (25.8, 33.5)	30.8 (26.1, 35.4)	−1.1 (−6.9, 4.6)	1.0 (0.8, 1.1)
No Cytopenia History				
Anemia				
3 months	1.6 (0.9, 2.4)	3.1 (1.6, 4.6)	−1.4 (−3.0, 0.2)	0.6 (0.2, 0.9)
6 months	2.9 (1.9, 4.0)	4.0 (2.4, 5.6)	−1.1 (−2.9, 0.8)	0.8 (0.3, 1.2)
12 months	4.3 (3.0, 5.5)	4.6 (2.8, 6.4)	−0.3 (−2.5, 1.9)	1.0 (0.5, 1.5)
Leukopenia				
3 months	5.9 (4.9, 7.0)	6.4 (5.2, 7.7)	−0.5 (−2.1, 1.2)	0.9 (0.7, 1.2)
6 months	8.6 (7.3, 9.9)	7.8 (6.3, 9.2)	0.8 (−1.1, 2.8)	1.1 (0.8, 1.4)
12 months	11.9 (10.3, 13.5)	8.9 (7.1, 10.7)	3.0 (0.5, 5.4)	1.4 (1.0, 1.7)
Neutropenia				
3 months	8.2 (7.1, 9.2)	6.6 (5.4, 7.8)	1.6 (−0.1, 3.2)	1.2 (0.9, 1.6)
6 months	12.5 (11.1, 13.9)	8.1 (6.7, 9.5)	4.4 (2.4, 6.4)	1.6 (1.2, 1.9)
12 months	17.5 (16.0, 19.1)	10.8 (9.0, 12.6)	6.7 (4.5, 9.0)	1.6 (1.3, 1.9)
Lymphocytopenia				
3 months	12.6 (11.3, 14.0)	14.6 (12.8, 16.3)	−1.9 (−4.2, 0.3)	0.9 (0.7, 1.0)
6 months	16.4 (14.9, 18.0)	18.3 (16.2, 20.4)	−1.9 (−4.6, 0.8)	0.9 (0.8, 1.0)
12 months	20.6 (18.7, 22.4)	22.4 (19.9, 24.9)	−1.8 (−5.2, 1.5)	0.9 (0.8, 1.1)
Thrombocytopenia				
3 months	3.0 (2.2, 3.7)	6.3 (5.0, 7.6)	−3.3 (−4.8, −1.8)	0.5 (0.3, 0.6)
6 months	6.1 (5.0, 7.3)	7.7 (6.3, 9.0)	−1.5 (−3.4, 0.3)	0.8 (0.6, 1.0)
12 months	8.4 (7.0, 9.8)	8.9 (7.4, 10.4)	−0.5 (−2.6, 1.6)	1.0 (0.7, 1.2)

The risks of all severe cytopenias following second LOT initiation according to first and/or second LOT IMiD exposure are displayed in **Figure 21** and **Table 24**. All cytopenia risks were substantially lower among those with no recent cytopenia history. There was no evidence of additive or multiplicative interaction between the first and second LOT IMiD exposure and cytopenia history on the risks of any of the severe cytopenias under study based on the stratified RDs and RRs at 3, 6, and 12 months.

Figure 21. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by exposure during the first line of therapy and according to recent history of the given cytopenia

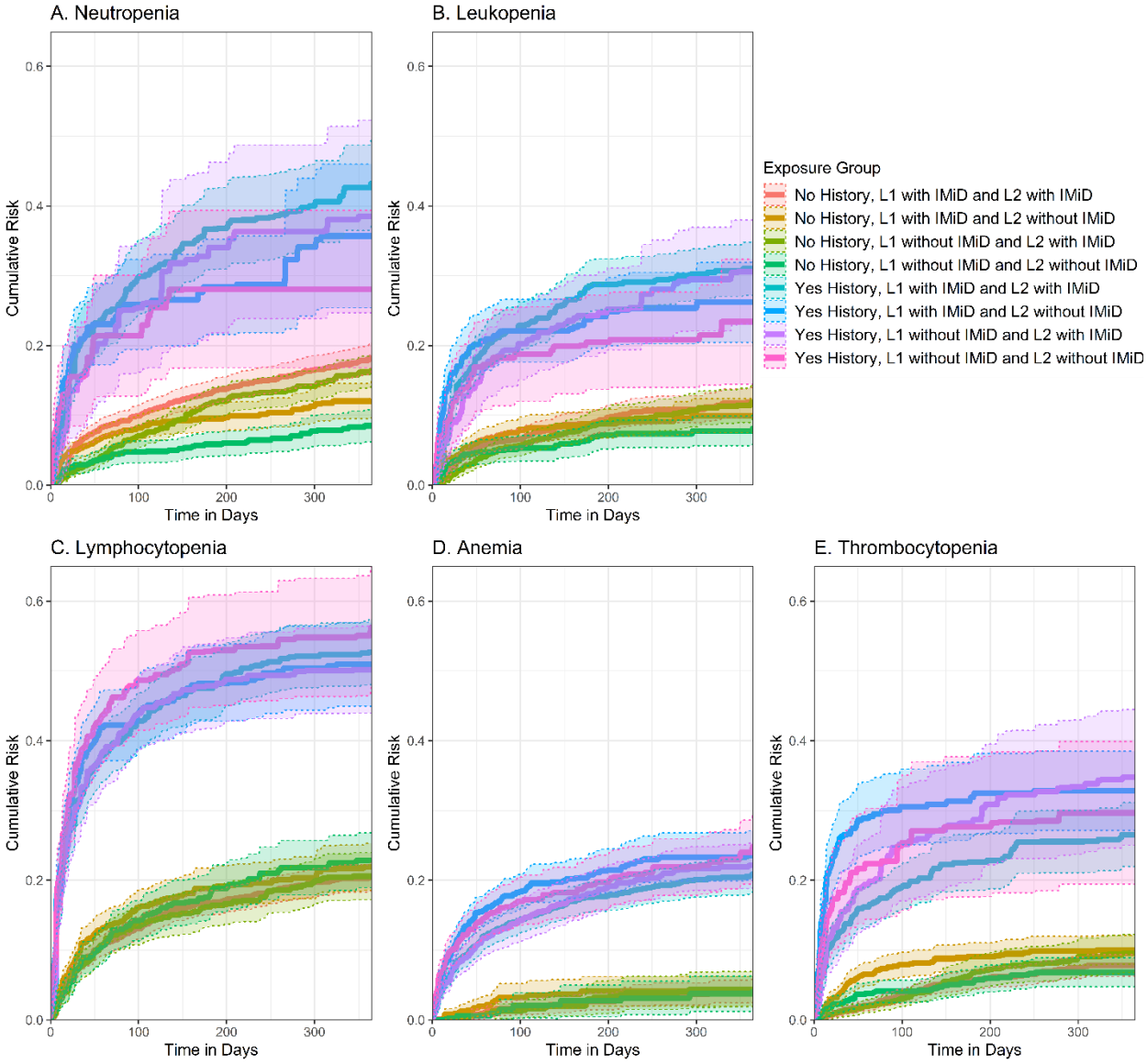


Table 24. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by first line of therapy exposure and according to recent history of the given cytopenia

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
Anemia				
Cytopenia History				
3 months				
Risk /100 (95% CI)	13.9 (11.9, 15.8)	17.7 (15.3, 20.2)	13.6 (10.8, 16.5)	16.2 (12.9, 19.4)
Stratified RD /100 (95% CI)	-3.9 (-7.1, -0.6)	Ref	-2.5 (-6.7, 1.7)	Ref
Stratified RR (95% CI)	0.8 (0.6, 0.9)	Ref	0.9 (0.6, 1.1)	Ref
Common Ref RD /100 (95% CI)	-2.3 (-6.2, 1.7)	1.6 (-3.0, 6.1)	-2.5 (-6.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.6, 1.1)	1.1 (0.8, 1.4)	0.9 (0.6, 1.1)	Ref
6 months				
Risk /100 (95% CI)	17.6 (15.5, 19.7)	20.8 (17.8, 23.8)	18.1 (14.9, 21.2)	19.3 (15.4, 23.1)
Stratified RD /100 (95% CI)	-3.2 (-7.1, 0.7)	Ref	-1.2 (-6.1, 3.7)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	0.9 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	-1.7 (-6.1, 2.8)	1.6 (-3.9, 7.0)	-1.2 (-6.1, 3.7)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.1 (0.8, 1.4)	0.9 (0.7, 1.2)	Ref
12 months				
Risk /100 (95% CI)	20.8 (18.3, 23.4)	23.5 (20.0, 27.1)	22.1 (18.9, 25.3)	24.8 (19.9, 29.8)
Stratified RD /100 (95% CI)	-2.7 (-7.1, 1.7)	Ref	-2.7 (-8.3, 2.9)	Ref
Stratified RR (95% CI)	0.9 (0.7, 1.1)	Ref	0.9 (0.7, 1.1)	Ref
Common Ref RD /100 (95% CI)	-4.0 (-9.4, 1.4)	-1.3 (-8.0, 5.4)	-2.7 (-8.3, 2.9)	Ref
Common Ref RR (95% CI)	0.8 (0.7, 1.0)	1.0 (0.7, 1.2)	0.9 (0.7, 1.1)	Ref
No Cytopenia History				
3 months				
Risk /100 (95% CI)	1.6 (0.6, 2.6)	3.2 (1.3, 5.2)	1.2 (0.2, 2.3)	1.5 (0.1, 2.9)
Stratified RD /100 (95% CI)	-1.6 (-3.8, 0.5)	Ref	-0.3 (-2.2, 1.6)	Ref
Stratified RR (95% CI)	0.6 (0.0, 1.1)	Ref	1.1 (-0.9, 3.1)	Ref
Common Ref RD /100 (95% CI)	0.1 (-1.7, 1.8)	1.7 (-0.8, 4.2)	-0.3 (-2.2, 1.6)	Ref
Common Ref RR (95% CI)	1.4 (-1.4, 4.3)	2.8 (-1.5, 7.1)	1.1 (-0.9, 3.1)	Ref
6 months				
Risk /100 (95% CI)	2.6 (1.4, 3.8)	4.1 (1.9, 6.2)	2.9 (0.7, 5.2)	2.7 (0.5, 5.0)
Stratified RD /100 (95% CI)	-1.5 (-3.8, 0.9)	Ref	0.2 (-3.1, 3.5)	Ref
Stratified RR (95% CI)	0.7 (0.2, 1.2)	Ref	1.4 (-2.2, 5.1)	Ref
Common Ref RD /100 (95% CI)	-0.1 (-2.7, 2.5)	1.3 (-2.0, 4.7)	0.2 (-3.1, 3.5)	Ref
Common Ref RR (95% CI)	1.2 (-0.5, 2.9)	1.9 (-1.4, 5.2)	1.4 (-2.2, 5.1)	Ref
12 months				
Risk /100 (95% CI)	4.1 (2.5, 5.7)	4.1 (1.9, 6.2)	4.4 (1.8, 6.9)	4.3 (1.7, 7.0)
Stratified RD /100 (95% CI)	0.0 (-2.6, 2.7)	Ref	0.0 (-4.0, 4.0)	Ref
Stratified RR (95% CI)	1.1 (0.4, 1.8)	Ref	1.1 (-0.1, 2.4)	Ref
Common Ref RD /100 (95% CI)	-0.2 (-3.1, 2.7)	-0.2 (-3.8, 3.3)	0.0 (-4.0, 4.0)	Ref
Common Ref RR (95% CI)	1.0 (0.3, 1.8)	1.1 (0.1, 2.0)	1.1 (-0.1, 2.4)	Ref
Leukopenia				
Cytopenia History				
3 months				
Risk /100 (95% CI)	22.1 (18.8, 25.5)	22.1 (17.6, 26.6)	19.3 (14.2, 24.5)	18.3 (11.4, 25.1)
Stratified RD /100 (95% CI)	0.0 (−5.6, 5.7)	Ref	1.1 (−8.4, 10.5)	Ref
Stratified RR (95% CI)	1.0 (0.7, 1.3)	Ref	1.1 (0.5, 1.7)	Ref
Common Ref RD /100 (95% CI)	3.9 (−3.7, 11.5)	3.9 (−4.5, 12.3)	1.1 (−8.4, 10.5)	Ref
Common Ref RR (95% CI)	1.3 (0.7, 1.8)	1.3 (0.7, 1.8)	1.1 (0.5, 1.7)	Ref
6 months				
Risk /100 (95% CI)	28.6 (24.9, 32.2)	23.7 (19.2, 28.3)	24.3 (18.4, 30.1)	20.5 (13.7, 27.2)
Stratified RD /100 (95% CI)	4.9 (−0.9, 10.7)	Ref	3.8 (−6.0, 13.5)	Ref
Stratified RR (95% CI)	1.2 (0.9, 1.5)	Ref	1.2 (0.7, 1.8)	Ref
Common Ref RD /100 (95% CI)	8.1 (0.4, 15.8)	3.2 (−4.9, 11.4)	3.8 (−6.0, 13.5)	Ref
Common Ref RR (95% CI)	1.4 (0.9, 1.9)	1.2 (0.7, 1.6)	1.2 (0.7, 1.8)	Ref
12 months				
Risk /100 (95% CI)	31.0 (27.2, 34.8)	26.2 (20.5, 31.9)	30.5 (23.1, 38.0)	23.4 (14.5, 32.4)

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Stratified RD /100 (95% CI)	4.8 (−2.0, 11.6)	Ref	7.1 (−4.7, 19.0)	Ref
Stratified RR (95% CI)	1.2 (0.9, 1.5)	Ref	1.4 (0.7, 2.0)	Ref
Common Ref RD /100 (95% CI)	7.6 (−2.2, 17.3)	2.8 (−7.6, 13.2)	7.1 (−4.7, 19.0)	Ref
Common Ref RR (95% CI)	1.4 (0.8, 1.9)	1.2 (0.7, 1.6)	1.4 (0.7, 2.0)	Ref
No Cytopenia History				
3 months				
Risk /100 (95% CI)	6.5 (5.1, 7.9)	7.5 (5.7, 9.3)	5.4 (4.0, 6.8)	5.2 (3.4, 6.9)
Stratified RD /100 (95% CI)	−1.0 (−3.1, 1.2)	Ref	0.2 (−2.1, 2.6)	Ref
Stratified RR (95% CI)	0.9 (0.6, 1.2)	Ref	1.1 (0.6, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.4 (−0.9, 3.6)	2.3 (−0.3, 4.9)	0.2 (−2.1, 2.6)	Ref
Common Ref RR (95% CI)	1.3 (0.7, 1.9)	1.5 (0.8, 2.2)	1.1 (0.6, 1.6)	Ref
6 months				
Risk /100 (95% CI)	8.8 (7.1, 10.4)	8.8 (6.7, 10.9)	8.5 (6.5, 10.4)	6.7 (4.7, 8.8)
Stratified RD /100 (95% CI)	0.0 (−2.6, 2.6)	Ref	1.8 (−1.0, 4.5)	Ref
Stratified RR (95% CI)	1.0 (0.7, 1.3)	Ref	1.3 (0.8, 1.8)	Ref
Common Ref RD /100 (95% CI)	2.0 (−0.5, 4.6)	2.1 (−0.8, 4.9)	1.8 (−1.0, 4.5)	Ref
Common Ref RR (95% CI)	1.3 (0.8, 1.8)	1.3 (0.8, 1.9)	1.3 (0.8, 1.8)	Ref
12 months				
Risk /100 (95% CI)	11.9 (9.8, 14.0)	10.0 (7.5, 12.4)	12.1 (9.5, 14.6)	8.1 (5.9, 10.4)
Stratified RD /100 (95% CI)	1.9 (−1.3, 5.1)	Ref	4.0 (0.5, 7.4)	Ref
Stratified RR (95% CI)	1.2 (0.8, 1.6)	Ref	1.5 (1.0, 2.1)	Ref
Common Ref RD /100 (95% CI)	3.8 (0.7, 6.8)	1.8 (−1.3, 4.9)	4.0 (0.5, 7.4)	Ref
Common Ref RR (95% CI)	1.5 (1.0, 2.0)	1.2 (0.8, 1.7)	1.5 (1.0, 2.1)	Ref
Neutropenia				
Cytopenia History				
3 months				
Risk /100 (95% CI)	28.1 (22.9, 33.3)	25.9 (19.4, 32.3)	25.1 (15.9, 34.2)	21.4 (12.7, 30.1)
Stratified RD /100 (95% CI)	2.2 (−6.2, 10.6)	Ref	3.7 (−9.2, 16.6)	Ref
Stratified RR (95% CI)	1.1 (0.7, 1.5)	Ref	1.2 (0.5, 1.9)	Ref
Common Ref RD /100 (95% CI)	6.7 (−3.5, 16.9)	4.5 (−6.8, 15.7)	3.7 (−9.2, 16.6)	Ref
Common Ref RR (95% CI)	1.4 (0.7, 2.0)	1.3 (0.6, 2.0)	1.2 (0.5, 1.9)	Ref
6 months				
Risk /100 (95% CI)	36.7 (30.9, 42.5)	28.4 (21.6, 35.2)	34.0 (21.8, 46.3)	28.1 (16.8, 39.4)
Stratified RD /100 (95% CI)	8.3 (−0.9, 17.5)	Ref	5.9 (−11.2, 23.1)	Ref
Stratified RR (95% CI)	1.3 (0.9, 1.7)	Ref	1.3 (0.6, 2.0)	Ref
Common Ref RD /100 (95% CI)	8.6 (−4.6, 21.7)	0.3 (−12.9, 13.5)	5.9 (−11.2, 23.1)	Ref
Common Ref RR (95% CI)	1.4 (0.7, 2.0)	1.1 (0.5, 1.6)	1.3 (0.6, 2.0)	Ref
12 months				
Risk /100 (95% CI)	43.2 (37.1, 49.4)	35.7 (25.4, 46.0)	38.5 (24.7, 52.3)	28.1 (16.8, 39.4)
Stratified RD /100 (95% CI)	7.5 (−4.8, 19.8)	Ref	10.4 (−7.2, 28.0)	Ref
Stratified RR (95% CI)	1.2 (0.8, 1.6)	Ref	1.4 (0.7, 2.2)	Ref
Common Ref RD /100 (95% CI)	15.1 (1.5, 28.7)	7.6 (−7.9, 23.1)	10.4 (−7.2, 28.0)	Ref
Common Ref RR (95% CI)	1.6 (0.9, 2.4)	1.3 (0.6, 2.1)	1.4 (0.7, 2.2)	Ref
No Cytopenia History				
3 months				
Risk /100 (95% CI)	9.4 (8.0, 10.8)	7.8 (6.1, 9.6)	6.5 (4.9, 8.0)	4.8 (3.2, 6.3)
Stratified RD /100 (95% CI)	1.6 (−0.7, 3.9)	Ref	1.7 (−0.5, 4.0)	Ref
Stratified RR (95% CI)	1.2 (0.9, 1.6)	Ref	1.4 (0.8, 2.0)	Ref
Common Ref RD /100 (95% CI)	4.6 (2.5, 6.8)	3.1 (0.7, 5.4)	1.7 (−0.5, 4.0)	Ref
Common Ref RR (95% CI)	2.0 (1.3, 2.8)	1.7 (1.0, 2.4)	1.4 (0.8, 2.0)	Ref
6 months				
Risk /100 (95% CI)	13.1 (11.3, 14.9)	9.5 (7.6, 11.4)	11.6 (9.5, 13.8)	5.9 (4.1, 7.6)
Stratified RD /100 (95% CI)	3.6 (1.0, 6.2)	Ref	5.8 (3.0, 8.6)	Ref
Stratified RR (95% CI)	1.4 (1.0, 1.7)	Ref	2.0 (1.3, 2.8)	Ref
Common Ref RD /100 (95% CI)	7.2 (4.8, 9.7)	3.7 (1.2, 6.1)	5.8 (3.0, 8.6)	Ref
Common Ref RR (95% CI)	2.3 (1.5, 3.1)	1.7 (1.1, 2.3)	2.0 (1.3, 2.8)	Ref
12 months				
Risk /100 (95% CI)	18.4 (16.4, 20.5)	12.4 (9.8, 15.0)	16.4 (14.1, 18.6)	8.5 (6.2, 10.8)
Stratified RD /100 (95% CI)	6.0 (2.7, 9.4)	Ref	7.9 (4.8, 11.0)	Ref
Stratified RR (95% CI)	1.5 (1.1, 1.9)	Ref	2.0 (1.4, 2.6)	Ref
Common Ref RD /100 (95% CI)	9.9 (6.7, 13.1)	3.9 (0.5, 7.3)	7.9 (4.8, 11.0)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Common Ref RR (95% CI)	2.2 (1.5, 2.9)	1.5 (1.0, 2.0)	2.0 (1.4, 2.6)	Ref
Lymphocytopenia				
Cytopenia History				
3 months				
Risk /100 (95% CI)	41.0 (37.0, 45.0)	42.3 (37.2, 47.3)	42.2 (37.1, 47.4)	47.8 (40.6, 55.1)
Stratified RD /100 (95% CI)	−1.3 (−8.0, 5.4)	Ref	−5.6 (−15.1, 3.9)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.7, 1.1)	Ref
Common Ref RD /100 (95% CI)	−6.9 (−15.9, 2.2)	−5.6 (−14.2, 3.1)	−5.6 (−15.1, 3.9)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	Ref
6 months				
Risk /100 (95% CI)	47.5 (43.0, 52.1)	48.2 (42.8, 53.6)	47.8 (41.8, 53.9)	52.8 (44.8, 60.9)
Stratified RD /100 (95% CI)	−0.7 (−8.0, 6.6)	Ref	−5.0 (−15.2, 5.2)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.7, 1.1)	Ref
Common Ref RD /100 (95% CI)	−5.3 (−15.1, 4.5)	−4.6 (−13.9, 4.7)	−5.0 (−15.2, 5.2)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)	Ref
12 months				
Risk /100 (95% CI)	52.7 (48.1, 57.4)	50.9 (45.0, 56.9)	50.2 (44.0, 56.4)	56.2 (47.6, 64.9)
Stratified RD /100 (95% CI)	1.8 (−5.9, 9.5)	Ref	−6.1 (−16.8, 4.6)	Ref
Stratified RR (95% CI)	1.0 (0.9, 1.2)	Ref	0.9 (0.7, 1.1)	Ref
Common Ref RD /100 (95% CI)	−3.5 (−13.5, 6.4)	−5.3 (−15.8, 5.2)	−6.1 (−16.8, 4.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	Ref
No Cytopenia History				
3 months				
Risk /100 (95% CI)	12.6 (10.9, 14.2)	15.0 (12.5, 17.4)	12.9 (10.3, 15.5)	13.7 (10.8, 16.6)
Stratified RD /100 (95% CI)	−2.4 (−5.4, 0.6)	Ref	−0.8 (−4.6, 3.1)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−1.1 (−4.4, 2.1)	1.3 (−2.8, 5.4)	−0.8 (−4.6, 3.1)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.2)	1.1 (0.8, 1.4)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	16.8 (15.0, 18.5)	18.8 (15.9, 21.7)	16.2 (13.3, 19.1)	17.5 (14.2, 20.9)
Stratified RD /100 (95% CI)	−2.1 (−5.5, 1.4)	Ref	−1.3 (−5.5, 2.9)	Ref
Stratified RR (95% CI)	0.9 (0.7, 1.1)	Ref	0.9 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−0.8 (−4.4, 2.9)	1.3 (−3.3, 5.9)	−1.3 (−5.5, 2.9)	Ref
Common Ref RR (95% CI)	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	0.9 (0.7, 1.2)	Ref
12 months				
Risk /100 (95% CI)	20.5 (18.5, 22.5)	21.9 (18.6, 25.3)	20.6 (17.2, 24.0)	22.9 (19.0, 26.8)
Stratified RD /100 (95% CI)	−1.5 (−5.6, 2.6)	Ref	−2.3 (−7.3, 2.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.7, 1.1)	Ref
Common Ref RD /100 (95% CI)	−2.4 (−6.9, 2.1)	−0.9 (−6.2, 4.4)	−2.3 (−7.3, 2.7)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.7, 1.2)	0.9 (0.7, 1.1)	Ref
Thrombocytopenia				
Cytopenia History				
3 months				
Risk /100 (95% CI)	18.3 (15.2, 21.4)	30.0 (24.8, 35.3)	24.7 (16.5, 32.9)	22.8 (14.8, 30.8)
Stratified RD /100 (95% CI)	−11.8 (−17.9, −5.6)	Ref	1.9 (−9.5, 13.3)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.8)	Ref	1.1 (0.6, 1.7)	Ref
Common Ref RD /100 (95% CI)	−4.5 (−12.9, 3.9)	7.3 (−2.1, 16.6)	1.9 (−9.5, 13.3)	Ref
Common Ref RR (95% CI)	0.8 (0.5, 1.1)	1.4 (0.8, 1.9)	1.1 (0.6, 1.7)	Ref
6 months				
Risk /100 (95% CI)	22.6 (18.6, 26.6)	31.9 (26.2, 37.5)	28.2 (19.6, 36.7)	27.7 (17.6, 37.7)
Stratified RD /100 (95% CI)	−9.3 (−16.3, −2.3)	Ref	0.5 (−13.1, 14.1)	Ref
Stratified RR (95% CI)	0.7 (0.5, 0.9)	Ref	1.1 (0.5, 1.6)	Ref
Common Ref RD /100 (95% CI)	−5.1 (−15.4, 5.3)	4.2 (−7.4, 15.8)	0.5 (−13.1, 14.1)	Ref
Common Ref RR (95% CI)	0.8 (0.5, 1.2)	1.2 (0.7, 1.7)	1.1 (0.5, 1.6)	Ref
12 months				
Risk /100 (95% CI)	26.5 (21.9, 31.1)	32.8 (27.1, 38.5)	34.8 (25.0, 44.5)	29.7 (19.4, 39.9)
Stratified RD /100 (95% CI)	−6.3 (−13.7, 1.1)	Ref	5.1 (−10.1, 20.3)	Ref
Stratified RR (95% CI)	0.8 (0.6, 1.0)	Ref	1.2 (0.6, 1.8)	Ref
Common Ref RD /100 (95% CI)	−3.1 (−13.9, 7.6)	3.2 (−8.4, 14.7)	5.1 (−10.1, 20.3)	Ref
Common Ref RR (95% CI)	0.9 (0.6, 1.3)	1.1 (0.7, 1.6)	1.2 (0.6, 1.8)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
No Cytopenia History				
3 months				
Risk /100 (95% CI)	3.1 (2.1, 4.0)	7.7 (5.9, 9.5)	2.7 (1.6, 3.7)	4.1 (2.5, 5.7)
Stratified RD /100 (95% CI)	−4.6 (−6.6, −2.6)	Ref	−1.4 (−3.3, 0.5)	Ref
Stratified RR (95% CI)	0.4 (0.3, 0.6)	Ref	0.7 (0.3, 1.0)	Ref
Common Ref RD /100 (95% CI)	−1.0 (−2.9, 0.9)	3.6 (1.2, 6.0)	−1.4 (−3.3, 0.5)	Ref
Common Ref RR (95% CI)	0.8 (0.4, 1.2)	2.0 (1.0, 2.9)	0.7 (0.3, 1.0)	Ref
6 months				
Risk /100 (95% CI)	5.8 (4.4, 7.2)	9.0 (7.0, 11.0)	6.8 (4.4, 9.1)	5.3 (3.5, 7.1)
Stratified RD /100 (95% CI)	−3.3 (−5.7, −0.8)	Ref	1.5 (−1.5, 4.4)	Ref
Stratified RR (95% CI)	0.6 (0.4, 0.9)	Ref	1.3 (0.7, 2.0)	Ref
Common Ref RD /100 (95% CI)	0.5 (−1.8, 2.7)	3.7 (1.0, 6.5)	1.5 (−1.5, 4.4)	Ref
Common Ref RR (95% CI)	1.1 (0.6, 1.6)	1.8 (1.0, 2.6)	1.3 (0.7, 2.0)	Ref
12 months				
Risk /100 (95% CI)	7.8 (6.3, 9.4)	10.0 (8.0, 12.1)	9.5 (6.8, 12.3)	6.8 (4.7, 8.9)
Stratified RD /100 (95% CI)	−2.2 (−4.8, 0.4)	Ref	2.7 (−0.7, 6.1)	Ref
Stratified RR (95% CI)	0.8 (0.6, 1.0)	Ref	1.4 (0.8, 2.0)	Ref
Common Ref RD /100 (95% CI)	1.0 (−1.6, 3.6)	3.2 (0.3, 6.1)	2.7 (−0.7, 6.1)	Ref
Common Ref RR (95% CI)	1.2 (0.7, 1.6)	1.5 (0.9, 2.1)	1.4 (0.8, 2.0)	Ref

The associations between sequential, versus never, exposure with neutropenia and leukopenia were even stronger among those with a history of the given cytopenia but were attenuated for those with no history (**Figure 21A–B**). There were no substantial differences in the risks of cytopenias not related to white blood cells (anemia, thrombocytopenia) among those sequentially, versus never, exposed to IMiDs among the cytopenia-history-stratified groups (**Figure 21D–E**). Among those with no recent histories of anemia or thrombocytopenia, the post-second LOT risks of these cytopenias did not exceed 10%, even for those sequentially exposed.

Treatment Effect according to Age

The cumulative incidence of each cytopenia among those exposed versus unexposed to IMiDs during the second LOT stratified according to age (75+ versus <75) are displayed in **Figure 22** and **Table 25**. Stratification by age did not appear to alter the relative risks of any cytopenias for those exposed, versus unexposed, to IMiDs during the second LOT. The cumulative risks of each cytopenia were not necessarily higher among those age 75+ compared to those age <75.

Figure 22. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, according to age

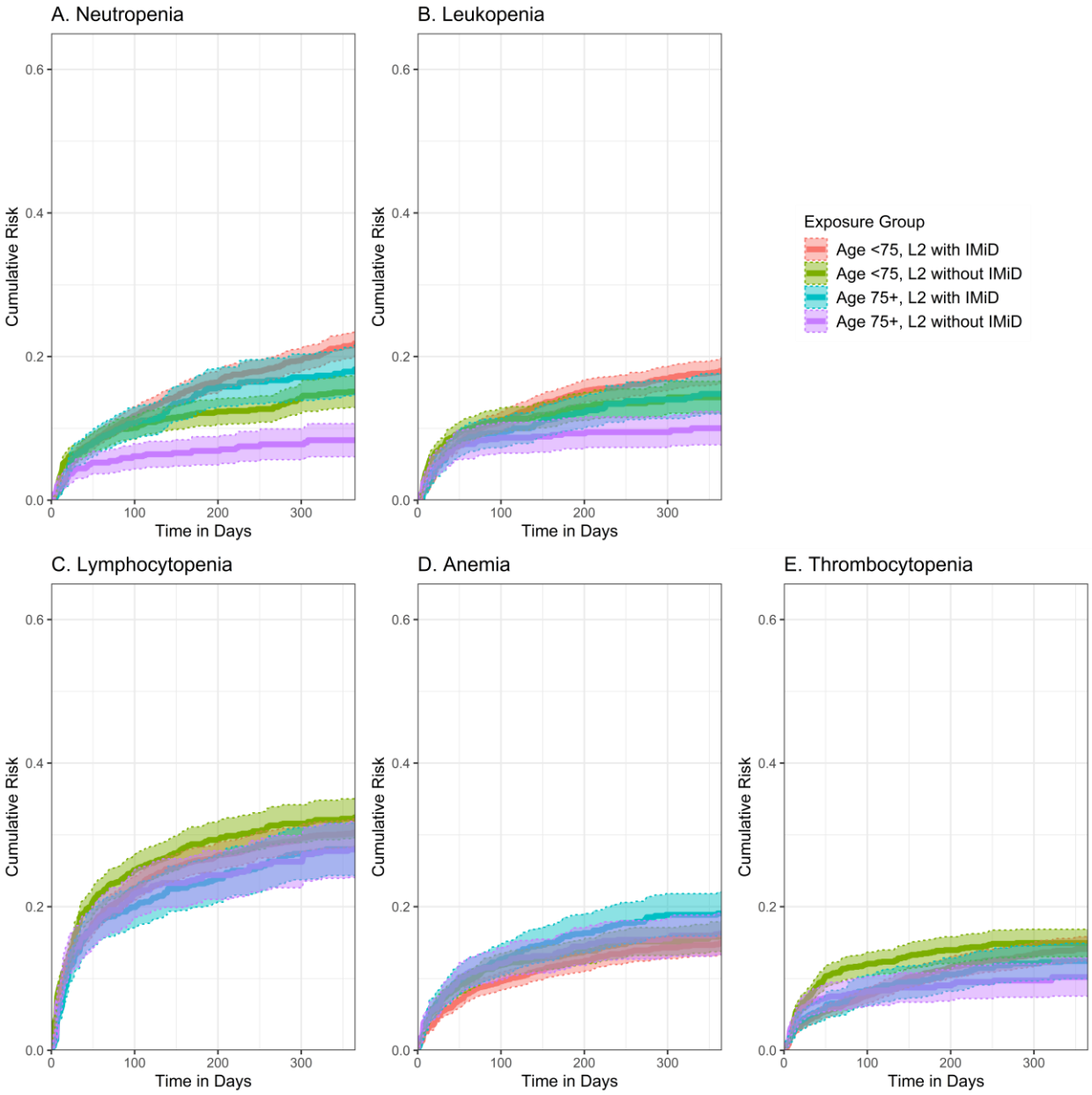


Table 25. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by age

	Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Not Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Risk Ratio (95% CI)
Age 75+				
Anemia				
3 months	12.2 (10.1, 14.4)	11.5 (9.4, 13.7)	0.7 (−2.2, 3.6)	1.1 (0.8, 1.3)
6 months	15.9 (13.2, 18.5)	13.9 (11.4, 16.4)	2.0 (−1.5, 5.5)	1.2 (0.9, 1.4)
12 months	19.1 (16.1, 22.0)	16.6 (13.5, 19.8)	2.5 (−1.7, 6.6)	1.2 (0.9, 1.4)
Leukopenia				
3 months	9.3 (7.3, 11.4)	8.5 (6.4, 10.6)	0.8 (−1.9, 3.6)	1.1 (0.8, 1.5)
6 months	11.8 (9.6, 14.0)	9.3 (7.2, 11.4)	2.5 (−0.3, 5.3)	1.3 (0.9, 1.6)
12 months	14.8 (12.0, 17.6)	10.0 (7.7, 12.3)	4.8 (1.2, 8.4)	1.5 (1.0, 2.0)
Neutropenia				
3 months	10.3 (8.2, 12.5)	5.9 (4.2, 7.5)	4.5 (1.9, 7.0)	1.8 (1.2, 2.4)
6 months	14.8 (12.3, 17.4)	6.9 (4.9, 8.8)	8.0 (4.8, 11.1)	2.2 (1.5, 2.9)
12 months	18.2 (14.8, 21.6)	8.4 (6.0, 10.7)	9.9 (5.9, 13.9)	2.2 (1.5, 3.0)
Lymphocytopenia				
3 months	19.3 (16.4, 22.2)	20.3 (17.1, 23.5)	−1.0 (−5.0, 3.0)	1.0 (0.8, 1.1)
6 months	23.2 (20.0, 26.5)	23.9 (20.6, 27.3)	−0.7 (−5.1, 3.7)	1.0 (0.8, 1.2)
12 months	28.0 (24.4, 31.6)	28.0 (24.1, 31.9)	0.0 (−5.1, 5.2)	1.0 (0.8, 1.2)
Thrombocytopenia				
3 months	8.2 (6.1, 10.3)	8.0 (6.0, 10.0)	0.2 (−2.5, 2.9)	1.0 (0.7, 1.4)
6 months	10.1 (7.8, 12.4)	8.7 (6.7, 10.8)	1.4 (−1.5, 4.3)	1.2 (0.8, 1.5)
12 months	12.4 (10.0, 14.9)	10.2 (7.6, 12.8)	2.2 (−1.1, 5.6)	1.2 (0.9, 1.6)
Age <75				
Anemia				
3 months	9.2 (8.0, 10.4)	11.3 (9.7, 12.9)	−2.2 (−4.0, −0.3)	0.8 (0.7, 1.0)
6 months	12.0 (10.6, 13.4)	13.4 (11.7, 15.1)	−1.3 (−3.4, 0.7)	0.9 (0.8, 1.0)
12 months	14.9 (13.3, 16.5)	15.9 (13.8, 18.0)	−1.0 (−3.5, 1.5)	0.9 (0.8, 1.1)
Leukopenia				
3 months	10.6 (9.3, 11.8)	10.9 (9.2, 12.5)	−0.3 (−2.3, 1.7)	1.0 (0.8, 1.2)
6 months	14.4 (13.0, 15.9)	12.7 (10.8, 14.5)	1.8 (−0.6, 4.1)	1.1 (0.9, 1.4)
12 months	18.1 (16.4, 19.8)	14.4 (12.2, 16.7)	3.7 (0.8, 6.5)	1.3 (1.0, 1.5)
Neutropenia				
3 months	11.0 (9.7, 12.2)	9.9 (8.3, 11.5)	1.0 (−1.0, 3.1)	1.1 (0.9, 1.3)
6 months	16.0 (14.5, 17.5)	12.1 (10.3, 13.9)	3.8 (1.4, 6.3)	1.3 (1.1, 1.6)
12 months	21.9 (20.2, 23.7)	15.4 (13.1, 17.6)	6.6 (3.7, 9.4)	1.4 (1.2, 1.7)
Lymphocytopenia				
3 months	21.6 (19.9, 23.2)	24.3 (22.1, 26.4)	−2.7 (−5.4, 0.0)	0.9 (0.8, 1.0)
6 months	26.5 (24.6, 28.3)	28.7 (26.3, 31.1)	−2.2 (−5.4, 0.9)	0.9 (0.8, 1.0)
12 months	30.3 (28.4, 32.2)	32.4 (29.7, 35.2)	−2.1 (−5.6, 1.3)	0.9 (0.8, 1.0)
Thrombocytopenia				
3 months	7.1 (6.1, 8.1)	11.7 (10.1, 13.3)	−4.6 (−6.4, −2.9)	0.6 (0.5, 0.7)
6 months	11.0 (9.6, 12.4)	13.7 (11.9, 15.5)	−2.7 (−4.9, −0.5)	0.8 (0.7, 0.9)
12 months	14.1 (12.4, 15.8)	14.9 (13.0, 16.9)	−0.8 (−3.3, 1.7)	0.9 (0.8, 1.1)

The cumulative incidence of each cytopenia according to IMiD exposure during the first and/or second LOTs stratified according to age (75+ versus <75) are displayed in **Figure 23** and **Table 26**. Stratification by age did not alter the relative risks of any cytopenias for those sequentially, versus never, exposed to IMiDs.

Figure 23. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by exposure during the first line of therapy and according to age

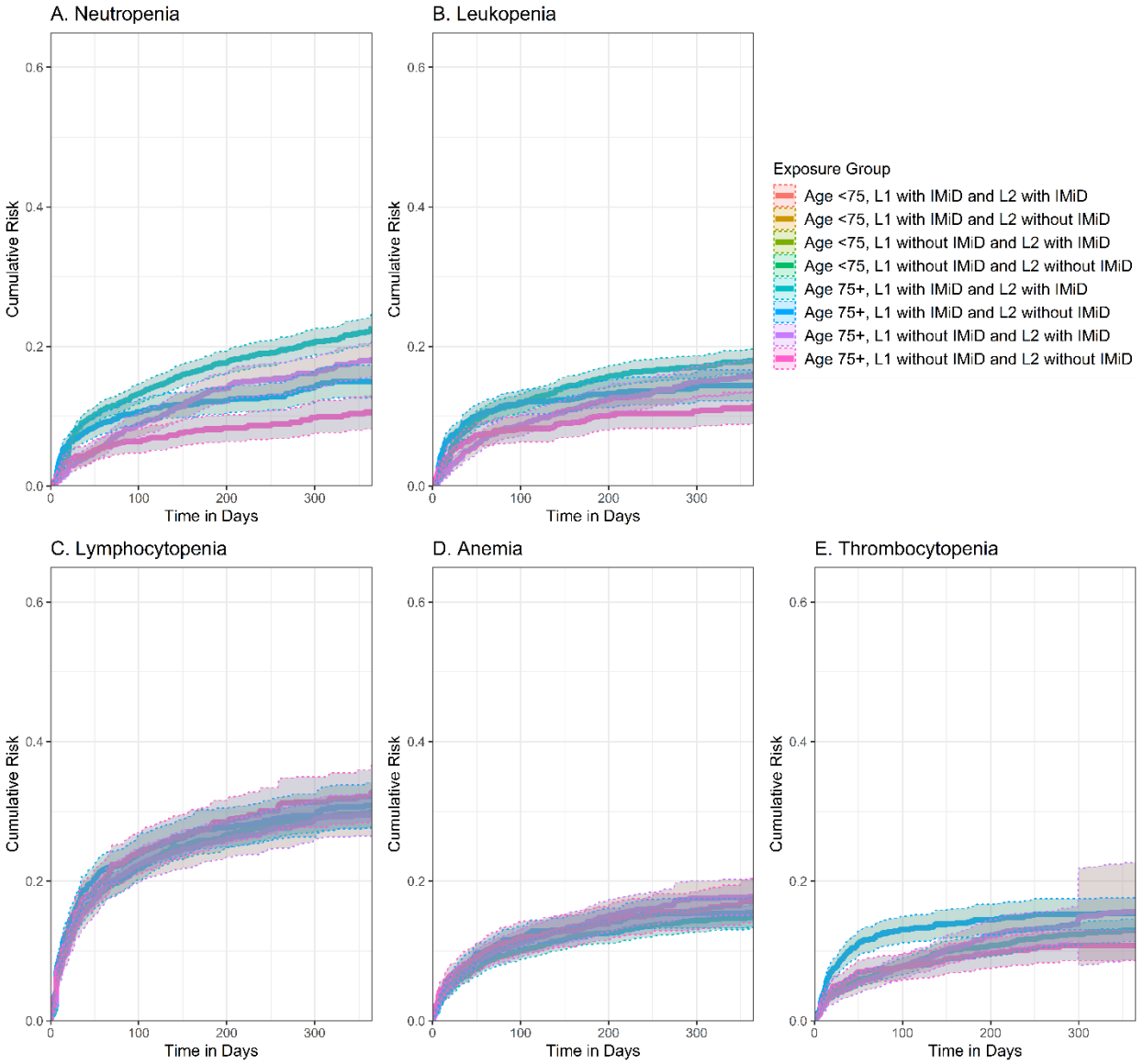


Table 26. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by first line of therapy exposure and according to age

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
Anemia				
Age 75+				
3 months				
Risk /100 (95% CI)	9.7 (8.4, 10.9)	11.6 (10.1, 13.1)	10.7 (8.8, 12.6)	11.2 (9.0, 13.5)
Stratified RD /100 (95% CI)	−1.9 (−3.8, −0.1)	Ref	−0.5 (−3.4, 2.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−4.1, 1.0)	0.4 (−2.3, 3.0)	−0.5 (−3.4, 2.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	12.4 (11.0, 13.9)	13.8 (12.0, 15.6)	14.2 (12.0, 16.4)	13.6 (11.2, 16.0)
Stratified RD /100 (95% CI)	−1.3 (−3.5, 0.8)	Ref	0.6 (−2.5, 3.8)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	1.1 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−1.2 (−3.9, 1.6)	0.2 (−2.7, 3.1)	0.6 (−2.5, 3.8)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	Ref
12 months				
Risk /100 (95% CI)	15.1 (13.3, 16.8)	15.5 (13.4, 17.7)	17.8 (15.2, 20.4)	17.7 (14.5, 20.9)
Stratified RD /100 (95% CI)	−0.5 (−2.9, 2.0)	Ref	0.2 (−4.0, 4.3)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	1.0 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.1, 0.9)	−2.1 (−5.9, 1.6)	0.2 (−4.0, 4.3)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	Ref
Age <75				
3 months				
Risk /100 (95% CI)	9.7 (8.4, 10.9)	11.6 (10.1, 13.1)	10.7 (8.8, 12.6)	11.2 (9.0, 13.5)
Stratified RD /100 (95% CI)	−1.9 (−3.8, −0.1)	Ref	−0.5 (−3.4, 2.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−4.1, 1.0)	0.4 (−2.3, 3.0)	−0.5 (−3.4, 2.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	12.4 (11.0, 13.9)	13.8 (12.0, 15.6)	14.2 (12.0, 16.4)	13.6 (11.2, 16.0)
Stratified RD /100 (95% CI)	−1.3 (−3.5, 0.8)	Ref	0.6 (−2.5, 3.8)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	1.1 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−1.2 (−3.9, 1.6)	0.2 (−2.7, 3.1)	0.6 (−2.5, 3.8)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	Ref
12 months				
Risk /100 (95% CI)	15.1 (13.3, 16.8)	15.5 (13.4, 17.7)	17.8 (15.2, 20.4)	17.7 (14.5, 20.9)
Stratified RD /100 (95% CI)	−0.5 (−2.9, 2.0)	Ref	0.2 (−4.0, 4.3)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	1.0 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.1, 0.9)	−2.1 (−5.9, 1.6)	0.2 (−4.0, 4.3)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	Ref
Leukopenia				
Age 75+				
3 months				
Risk /100 (95% CI)	11.5 (10.2, 12.9)	11.7 (9.9, 13.4)	8.4 (6.9, 9.8)	8.0 (6.1, 9.9)
Stratified RD /100 (95% CI)	−0.1 (−2.2, 2.0)	Ref	0.3 (−2.0, 2.7)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.7, 1.4)	Ref
Common Ref RD /100 (95% CI)	3.5 (1.3, 5.8)	3.7 (1.0, 6.3)	0.3 (−2.0, 2.7)	Ref
Common Ref RR (95% CI)	1.5 (1.1, 1.9)	1.5 (1.0, 1.9)	1.1 (0.7, 1.4)	Ref
6 months				
Risk /100 (95% CI)	15.0 (13.6, 16.5)	13.0 (11.1, 14.9)	11.8 (10.0, 13.7)	9.8 (7.7, 11.9)
Stratified RD /100 (95% CI)	2.0 (−0.3, 4.4)	Ref	2.0 (−0.7, 4.7)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.4)	Ref	1.2 (0.9, 1.5)	Ref
Common Ref RD /100 (95% CI)	5.2 (2.7, 7.7)	3.2 (0.4, 6.0)	2.0 (−0.7, 4.7)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (0.9, 1.5)	Ref
12 months				
Risk /100 (95% CI)	17.9 (16.2, 19.6)	14.4 (12.2, 16.6)	16.1 (13.7, 18.6)	11.5 (9.1, 13.9)

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Stratified RD /100 (95% CI)	3.5 (0.7, 6.3)	Ref	4.7 (1.2, 8.2)	Ref
Stratified RR (95% CI)	1.3 (1.0, 1.5)	Ref	1.4 (1.0, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.5 (3.6, 9.3)	3.0 (−0.2, 6.1)	4.7 (1.2, 8.2)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.6)	1.4 (1.0, 1.8)	Ref
Age <75				
3 months				
Risk /100 (95% CI)	11.5 (10.2, 12.9)	11.7 (9.9, 13.4)	8.4 (6.9, 9.8)	8.0 (6.1, 9.9)
Stratified RD /100 (95% CI)	−0.1 (−2.2, 2.0)	Ref	0.3 (−2.0, 2.7)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.7, 1.4)	Ref
Common Ref RD /100 (95% CI)	3.5 (1.3, 5.8)	3.7 (1.0, 6.3)	0.3 (−2.0, 2.7)	Ref
Common Ref RR (95% CI)	1.5 (1.1, 1.9)	1.5 (1.0, 1.9)	1.1 (0.7, 1.4)	Ref
6 months				
Risk /100 (95% CI)	15.0 (13.6, 16.5)	13.0 (11.1, 14.9)	11.8 (10.0, 13.7)	9.8 (7.7, 11.9)
Stratified RD /100 (95% CI)	2.0 (−0.3, 4.4)	Ref	2.0 (−0.7, 4.7)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.4)	Ref	1.2 (0.9, 1.5)	Ref
Common Ref RD /100 (95% CI)	5.2 (2.7, 7.7)	3.2 (0.4, 6.0)	2.0 (−0.7, 4.7)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (0.9, 1.5)	Ref
12 months				
Risk /100 (95% CI)	17.9 (16.2, 19.6)	14.4 (12.2, 16.6)	16.1 (13.7, 18.6)	11.5 (9.1, 13.9)
Stratified RD /100 (95% CI)	3.5 (0.7, 6.3)	Ref	4.7 (1.2, 8.2)	Ref
Stratified RR (95% CI)	1.3 (1.0, 1.5)	Ref	1.4 (1.0, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.5 (3.6, 9.3)	3.0 (−0.2, 6.1)	4.7 (1.2, 8.2)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.6)	1.4 (1.0, 1.8)	Ref
Neutropenia				
Age 75+				
3 months				
Risk /100 (95% CI)	12.5 (11.1, 13.8)	10.3 (8.6, 12.0)	8.2 (6.6, 9.9)	6.4 (4.7, 8.1)
Stratified RD /100 (95% CI)	2.2 (−0.1, 4.4)	Ref	1.8 (−0.5, 4.2)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.5)	Ref	1.3 (0.9, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.1 (4.0, 8.1)	3.9 (1.4, 6.3)	1.8 (−0.5, 4.2)	Ref
Common Ref RR (95% CI)	2.0 (1.4, 2.5)	1.6 (1.1, 2.2)	1.3 (0.9, 1.8)	Ref
6 months				
Risk /100 (95% CI)	17.0 (15.4, 18.6)	12.1 (10.3, 14.0)	13.6 (11.4, 15.8)	8.2 (6.2, 10.1)
Stratified RD /100 (95% CI)	4.9 (2.4, 7.4)	Ref	5.4 (2.5, 8.4)	Ref
Stratified RR (95% CI)	1.4 (1.1, 1.7)	Ref	1.7 (1.2, 2.2)	Ref
Common Ref RD /100 (95% CI)	8.8 (6.4, 11.3)	4.0 (1.5, 6.5)	5.4 (2.5, 8.4)	Ref
Common Ref RR (95% CI)	2.1 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.2, 2.2)	Ref
12 months				
Risk /100 (95% CI)	22.7 (20.7, 24.6)	15.3 (12.8, 17.7)	18.1 (15.7, 20.5)	10.6 (8.2, 12.9)
Stratified RD /100 (95% CI)	7.4 (4.3, 10.5)	Ref	7.5 (4.3, 10.8)	Ref
Stratified RR (95% CI)	1.5 (1.2, 1.8)	Ref	1.7 (1.3, 2.2)	Ref
Common Ref RD /100 (95% CI)	12.1 (9.0, 15.2)	4.7 (1.3, 8.1)	7.5 (4.3, 10.8)	Ref
Common Ref RR (95% CI)	2.2 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	Ref
Age <75				
3 months				
Risk /100 (95% CI)	12.5 (11.1, 13.8)	10.3 (8.6, 12.0)	8.2 (6.6, 9.9)	6.4 (4.7, 8.1)
Stratified RD /100 (95% CI)	2.2 (−0.1, 4.4)	Ref	1.8 (−0.5, 4.2)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.5)	Ref	1.3 (0.9, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.1 (4.0, 8.1)	3.9 (1.4, 6.3)	1.8 (−0.5, 4.2)	Ref
Common Ref RR (95% CI)	2.0 (1.4, 2.5)	1.6 (1.1, 2.2)	1.3 (0.9, 1.8)	Ref
6 months				
Risk /100 (95% CI)	17.0 (15.4, 18.6)	12.1 (10.3, 14.0)	13.6 (11.4, 15.8)	8.2 (6.2, 10.1)
Stratified RD /100 (95% CI)	4.9 (2.4, 7.4)	Ref	5.4 (2.5, 8.4)	Ref
Stratified RR (95% CI)	1.4 (1.1, 1.7)	Ref	1.7 (1.2, 2.2)	Ref
Common Ref RD /100 (95% CI)	8.8 (6.4, 11.3)	4.0 (1.5, 6.5)	5.4 (2.5, 8.4)	Ref
Common Ref RR (95% CI)	2.1 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.2, 2.2)	Ref
12 months				
Risk /100 (95% CI)	22.7 (20.7, 24.6)	15.3 (12.8, 17.7)	18.1 (15.7, 20.5)	10.6 (8.2, 12.9)
Stratified RD /100 (95% CI)	7.4 (4.3, 10.5)	Ref	7.5 (4.3, 10.8)	Ref
Stratified RR (95% CI)	1.5 (1.2, 1.8)	Ref	1.7 (1.3, 2.2)	Ref
Common Ref RD /100 (95% CI)	12.1 (9.0, 15.2)	4.7 (1.3, 8.1)	7.5 (4.3, 10.8)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Common Ref RR (95% CI)	2.2 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	Ref
Lymphocytopenia				
Age 75+				
3 months				
Risk /100 (95% CI)	20.8 (19.2, 22.5)	23.0 (20.7, 25.3)	21.4 (19.0, 23.8)	23.4 (20.5, 26.3)
Stratified RD /100 (95% CI)	−2.1 (−5.1, 0.8)	Ref	−2.0 (−5.7, 1.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.0)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.0, 0.8)	−0.4 (−4.3, 3.4)	−2.0 (−5.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	Ref
6 months				
Risk /100 (95% CI)	25.9 (23.9, 27.8)	27.5 (24.7, 30.2)	25.5 (22.8, 28.2)	27.5 (24.3, 30.6)
Stratified RD /100 (95% CI)	−1.6 (−5.2, 1.9)	Ref	−2.0 (−5.9, 1.9)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−5.3, 2.1)	0.0 (−4.4, 4.4)	−2.0 (−5.9, 1.9)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	Ref
12 months				
Risk /100 (95% CI)	29.9 (27.8, 32.0)	30.8 (27.6, 34.1)	29.5 (26.5, 32.5)	32.7 (28.8, 36.5)
Stratified RD /100 (95% CI)	−0.9 (−5.0, 3.1)	Ref	−3.2 (−8.0, 1.6)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.8, 1.0)	Ref
Common Ref RD /100 (95% CI)	−2.8 (−7.2, 1.7)	−1.8 (−7.0, 3.3)	−3.2 (−8.0, 1.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	Ref
Age <75				
3 months				
Risk /100 (95% CI)	20.8 (19.2, 22.5)	23.0 (20.7, 25.3)	21.4 (19.0, 23.8)	23.4 (20.5, 26.3)
Stratified RD /100 (95% CI)	−2.1 (−5.1, 0.8)	Ref	−2.0 (−5.7, 1.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.0)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.0, 0.8)	−0.4 (−4.3, 3.4)	−2.0 (−5.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	Ref
6 months				
Risk /100 (95% CI)	25.9 (23.9, 27.8)	27.5 (24.7, 30.2)	25.5 (22.8, 28.2)	27.5 (24.3, 30.6)
Stratified RD /100 (95% CI)	−1.6 (−5.2, 1.9)	Ref	−2.0 (−5.9, 1.9)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−5.3, 2.1)	0.0 (−4.4, 4.4)	−2.0 (−5.9, 1.9)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	Ref
12 months				
Risk /100 (95% CI)	29.9 (27.8, 32.0)	30.8 (27.6, 34.1)	29.5 (26.5, 32.5)	32.7 (28.8, 36.5)
Stratified RD /100 (95% CI)	−0.9 (−5.0, 3.1)	Ref	−3.2 (−8.0, 1.6)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.8, 1.0)	Ref
Common Ref RD /100 (95% CI)	−2.8 (−7.2, 1.7)	−1.8 (−7.0, 3.3)	−3.2 (−8.0, 1.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	Ref
Thrombocytopenia				
Age 75+				
3 months				
Risk /100 (95% CI)	7.4 (6.3, 8.4)	12.8 (11.0, 14.7)	7.4 (5.7, 9.0)	7.5 (5.7, 9.3)
Stratified RD /100 (95% CI)	−5.5 (−7.5, −3.4)	Ref	−0.1 (−2.5, 2.2)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.7)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	−0.1 (−2.2, 2.0)	5.3 (2.6, 8.0)	−0.1 (−2.5, 2.2)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.3)	1.7 (1.2, 2.2)	1.0 (0.7, 1.3)	Ref
6 months				
Risk /100 (95% CI)	10.5 (9.0, 11.9)	14.3 (12.2, 16.4)	11.4 (9.2, 13.6)	9.2 (7.1, 11.3)
Stratified RD /100 (95% CI)	−3.8 (−6.3, −1.4)	Ref	2.2 (−0.8, 5.1)	Ref
Stratified RR (95% CI)	0.7 (0.6, 0.9)	Ref	1.3 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.3 (−1.3, 3.9)	5.1 (2.0, 8.2)	2.2 (−0.8, 5.1)	Ref
Common Ref RR (95% CI)	1.2 (0.8, 1.5)	1.6 (1.1, 2.0)	1.3 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	13.0 (11.4, 14.6)	15.4 (13.2, 17.6)	15.6 (8.6, 22.6)	10.8 (8.6, 13.0)
Stratified RD /100 (95% CI)	−2.4 (−5.0, 0.2)	Ref	4.8 (−2.4, 12.0)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.5 (0.8, 2.1)	Ref
Common Ref RD /100 (95% CI)	2.2 (−0.5, 4.9)	4.6 (1.4, 7.8)	4.8 (−2.4, 12.0)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.4 (1.1, 1.8)	1.5 (0.8, 2.1)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Age <75				
3 months				
Risk /100 (95% CI)	7.4 (6.3, 8.4)	12.8 (11.0, 14.7)	7.4 (5.7, 9.0)	7.5 (5.7, 9.3)
Stratified RD /100 (95% CI)	−5.5 (−7.5, −3.4)	Ref	−0.1 (−2.5, 2.2)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.7)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	−0.1 (−2.2, 2.0)	5.3 (2.6, 8.0)	−0.1 (−2.5, 2.2)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.3)	1.7 (1.2, 2.2)	1.0 (0.7, 1.3)	Ref
6 months				
Risk /100 (95% CI)	10.5 (9.0, 11.9)	14.3 (12.2, 16.4)	11.4 (9.2, 13.6)	9.2 (7.1, 11.3)
Stratified RD /100 (95% CI)	−3.8 (−6.3, −1.4)	Ref	2.2 (−0.8, 5.1)	Ref
Stratified RR (95% CI)	0.7 (0.6, 0.9)	Ref	1.3 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.3 (−1.3, 3.9)	5.1 (2.0, 8.2)	2.2 (−0.8, 5.1)	Ref
Common Ref RR (95% CI)	1.2 (0.8, 1.5)	1.6 (1.1, 2.0)	1.3 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	13.0 (11.4, 14.6)	15.4 (13.2, 17.6)	15.6 (8.6, 22.6)	10.8 (8.6, 13.0)
Stratified RD /100 (95% CI)	−2.4 (−5.0, 0.2)	Ref	4.8 (−2.4, 12.0)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.5 (0.8, 2.1)	Ref
Common Ref RD /100 (95% CI)	2.2 (−0.5, 4.9)	4.6 (1.4, 7.8)	4.8 (−2.4, 12.0)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.4 (1.1, 1.8)	1.5 (0.8, 2.1)	Ref

Treatment Effect according to Cytogenetic Risk

The risks of each cytopenia associated with second LOT IMiD exposure were not different between patients with high versus standard cytogenetic risk at baseline (**Figure 24** and **Table 27**). The relative risks of each cytopenia for those exposed, versus unexposed, to IMiDs during the second LOT were not impacted by stratification on cytogenetic risk.

Figure 24. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, according to cytogenetic risk

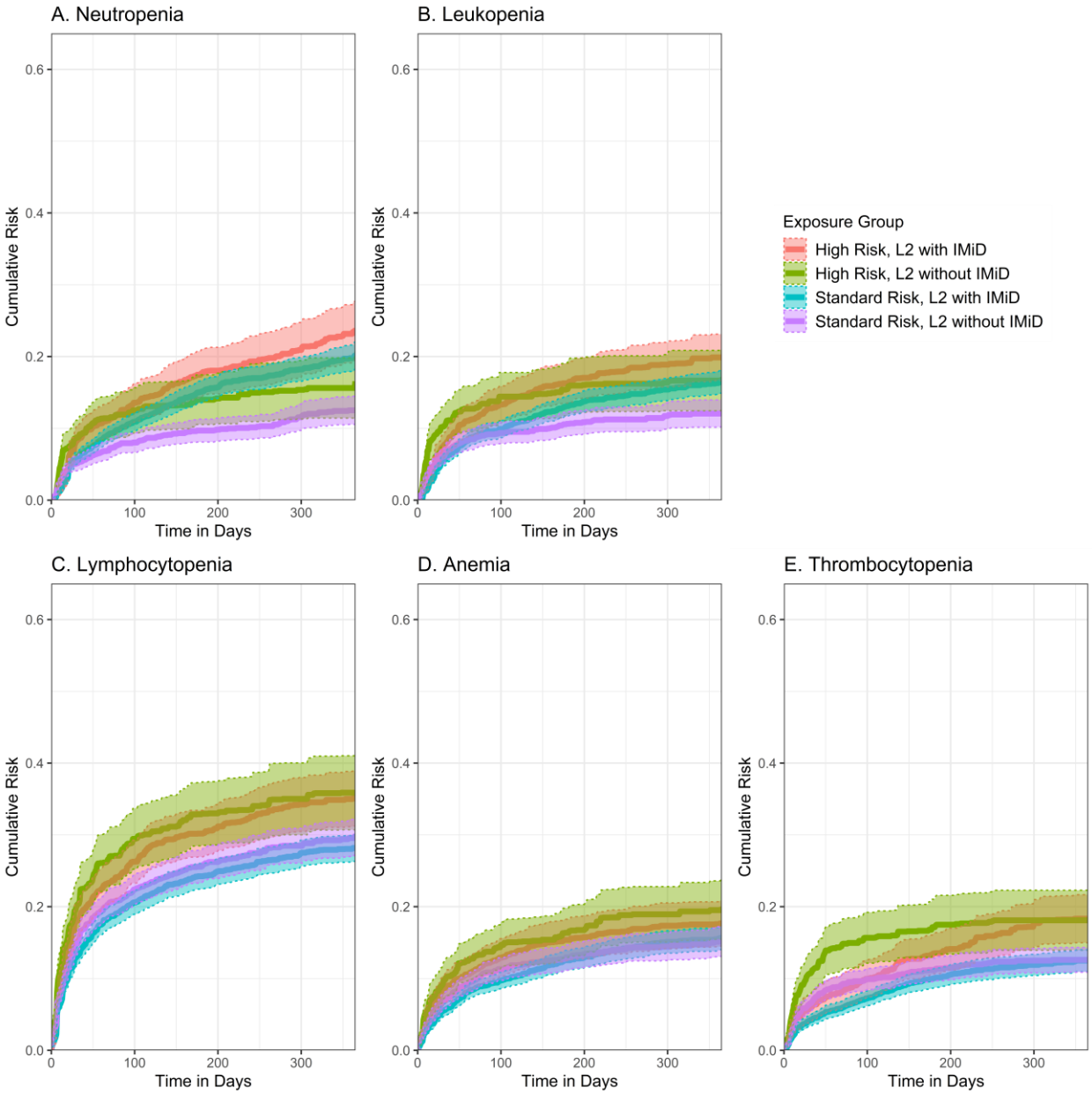


Table 27. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by cytogenetic risk

	Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Not Exposed to IMiDs during LOT 2 Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Risk Ratio (95% CI)
High Risk				
Anemia				
3 months	12.4 (9.8, 14.9)	13.7 (10.7, 16.8)	−1.4 (−4.8, 2.1)	0.9 (0.7, 1.2)
6 months	15.4 (12.5, 18.3)	16.4 (12.9, 19.8)	−1.0 (−5.1, 3.1)	0.9 (0.7, 1.2)
12 months	17.7 (14.5, 20.8)	19.6 (15.5, 23.7)	−1.9 (−6.7, 2.8)	0.9 (0.7, 1.1)
Leukopenia				
3 months	12.9 (10.3, 15.4)	13.8 (10.4, 17.1)	−0.9 (−5.0, 3.2)	0.9 (0.7, 1.2)
6 months	16.3 (13.5, 19.1)	15.5 (11.8, 19.1)	0.8 (−3.6, 5.3)	1.1 (0.8, 1.4)
12 months	19.9 (16.6, 23.1)	16.7 (12.5, 21.0)	3.1 (−2.0, 8.2)	1.2 (0.9, 1.6)
Neutropenia				
3 months	12.6 (10.0, 15.2)	11.9 (8.8, 15.1)	0.7 (−3.0, 4.4)	1.1 (0.7, 1.4)
6 months	17.7 (14.4, 21.0)	14.0 (10.5, 17.5)	3.7 (−0.5, 7.9)	1.3 (0.9, 1.6)
12 months	23.6 (19.6, 27.7)	16.5 (12.0, 21.0)	7.1 (1.5, 12.7)	1.5 (1.0, 1.9)
Lymphocytopenia				
3 months	24.9 (21.9, 27.9)	28.4 (24.3, 32.5)	−3.5 (−8.5, 1.5)	0.9 (0.7, 1.0)
6 months	30.2 (26.9, 33.4)	32.9 (28.5, 37.3)	−2.7 (−8.2, 2.8)	0.9 (0.8, 1.1)
12 months	35.1 (31.2, 38.9)	35.9 (30.7, 41.0)	−0.8 (−7.2, 5.6)	1.0 (0.8, 1.2)
Thrombocytopenia				
3 months	9.4 (6.8, 12.0)	15.2 (11.8, 18.7)	−5.8 (−9.9, −1.8)	0.6 (0.4, 0.8)
6 months	13.5 (10.7, 16.3)	17.1 (13.2, 21.0)	−3.7 (−8.1, 0.8)	0.8 (0.6, 1.0)
12 months	18.3 (15.0, 21.7)	18.1 (13.9, 22.3)	0.2 (−4.6, 5.1)	1.0 (0.7, 1.3)
Standard Risk				
Anemia				
3 months	9.3 (8.2, 10.5)	10.8 (9.3, 12.4)	−1.5 (−3.3, 0.3)	0.9 (0.7, 1.0)
6 months	12.5 (11.2, 13.9)	12.9 (11.2, 14.7)	−0.4 (−2.5, 1.7)	1.0 (0.8, 1.1)
12 months	15.6 (14.0, 17.3)	15.3 (13.2, 17.5)	0.3 (−2.3, 2.9)	1.0 (0.9, 1.2)
Leukopenia				
3 months	9.6 (8.4, 10.8)	9.2 (7.7, 10.6)	0.4 (−1.4, 2.3)	1.1 (0.8, 1.3)
6 months	13.1 (11.7, 14.5)	10.6 (9.0, 12.3)	2.5 (0.5, 4.5)	1.2 (1.0, 1.5)
12 months	16.6 (15.0, 18.2)	12.1 (10.2, 14.1)	4.4 (1.9, 6.9)	1.4 (1.1, 1.6)
Neutropenia				
3 months	10.3 (9.1, 11.5)	8.0 (6.6, 9.3)	2.4 (0.5, 4.2)	1.3 (1.0, 1.6)
6 months	15.1 (13.6, 16.7)	9.7 (8.1, 11.3)	5.4 (3.1, 7.7)	1.6 (1.3, 1.9)
12 months	20.2 (18.3, 22.1)	12.5 (10.6, 14.5)	7.7 (4.9, 10.4)	1.6 (1.3, 1.9)
Lymphocytopenia				
3 months	19.8 (18.2, 21.5)	21.4 (19.4, 23.4)	−1.6 (−4.2, 0.9)	0.9 (0.8, 1.0)
6 months	24.2 (22.5, 26.0)	25.6 (23.3, 27.8)	−1.3 (−4.2, 1.6)	0.9 (0.8, 1.1)
12 months	28.2 (26.3, 30.0)	29.8 (27.2, 32.4)	−1.6 (−4.8, 1.6)	0.9 (0.8, 1.1)
Thrombocytopenia				
3 months	6.8 (5.8, 7.9)	9.6 (8.2, 11.1)	−2.8 (−4.5, −1.2)	0.7 (0.6, 0.9)
6 months	10.0 (8.7, 11.4)	11.2 (9.5, 12.8)	−1.1 (−3.1, 0.8)	0.9 (0.7, 1.1)
12 months	12.5 (11.0, 14.0)	12.6 (10.9, 14.3)	−0.1 (−2.2, 2.0)	1.0 (0.8, 1.2)

The were no differences in the risks of each cytopenia associated with first and/or second LOT IMiD exposure (**Figure 25** and **Table 28**). The relative risks of each cytopenia for those sequentially, versus never, exposed to IMiDs were not impacted by stratification on cytogenetic risk.

Figure 25. Cumulative incidence of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by exposure during the first line of therapy and according to cytogenetic risk

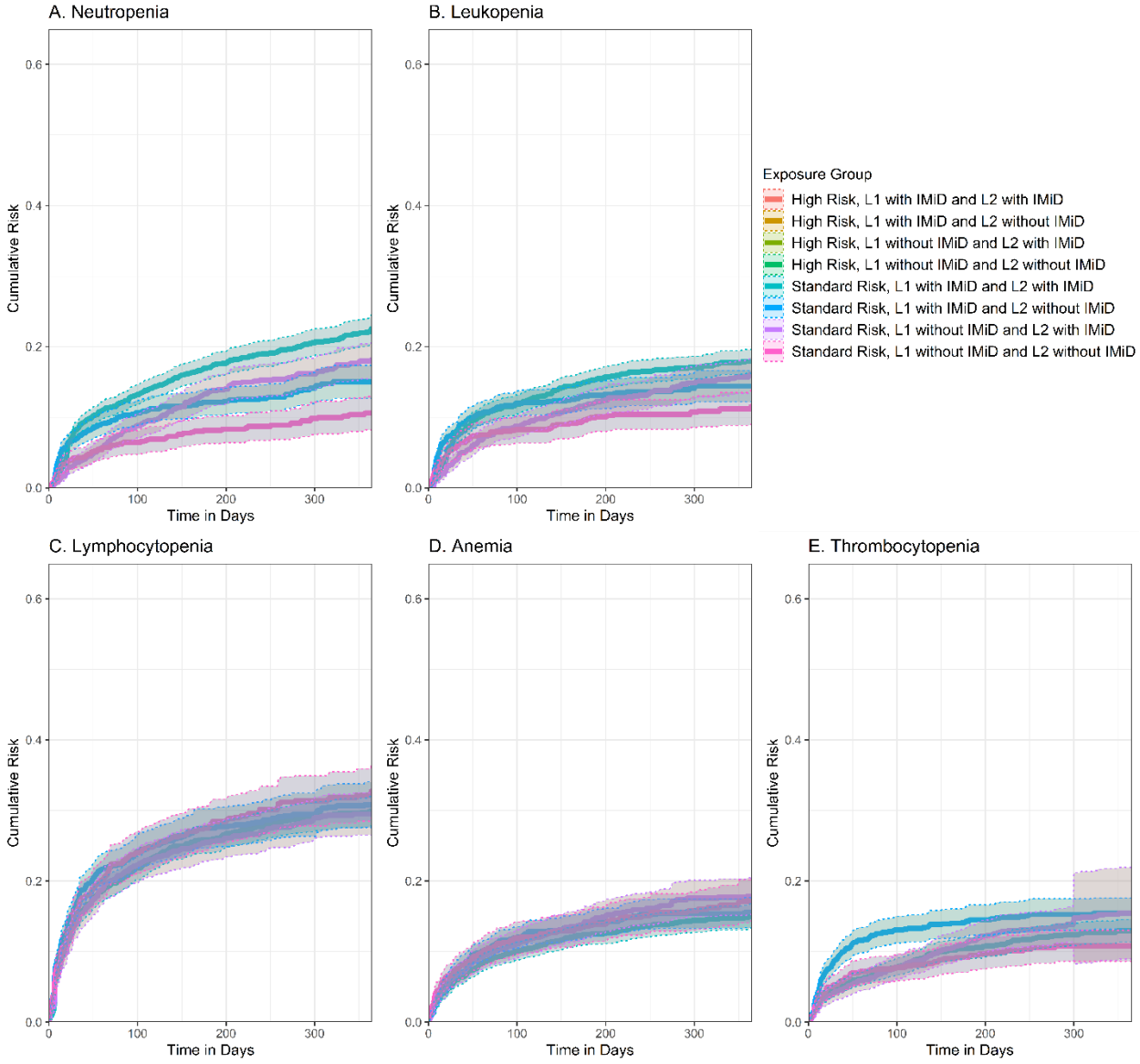


Table 28. Risks per 100, risk differences per 100, and risk ratios of cytopenias following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by first line of therapy exposure and according to cytogenetic risk

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
Anemia				
High Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	9.7 (8.4, 10.9)	11.6 (10.1, 13.1)	10.7 (8.8, 12.6)	11.2 (9.0, 13.5)
Stratified RD /100 (95% CI)	−1.9 (−3.8, −0.1)	Ref	−0.5 (−3.4, 2.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Re	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−4.1, 1.0)	0.4 (−2.3, 3.0)	−0.5 (−3.4, 2.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	12.4 (11.0, 13.9)	13.8 (12.0, 15.6)	14.2 (12.0, 16.4)	13.6 (11.2, 15.9)
Stratified RD /100 (95% CI)	−1.4 (−3.5, 0.8)	Ref	0.6 (−2.5, 3.8)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	1.1 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−1.1 (−3.9, 1.6)	0.2 (−2.7, 3.1)	0.6 (−2.5, 3.8)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	Ref
12 months				
Risk /100 (95% CI)	15.1 (13.4, 16.8)	15.5 (13.4, 17.7)	17.8 (15.2, 20.4)	17.6 (14.4, 20.8)
Stratified RD /100 (95% CI)	−0.4 (−2.9, 2.0)	Ref	0.2 (−4.0, 4.4)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	1.0 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.1, 0.9)	−2.1 (−5.9, 1.6)	0.2 (−4.0, 4.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	Ref
Standard Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	9.7 (8.4, 10.9)	11.6 (10.1, 13.1)	10.7 (8.8, 12.6)	11.2 (9.0, 13.5)
Stratified RD /100 (95% CI)	−1.9 (−3.8, −0.1)	Ref	−0.5 (−3.4, 2.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.0 (0.7, 1.2)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−4.1, 1.0)	0.4 (−2.3, 3.0)	−0.5 (−3.4, 2.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.2)	Ref
6 months				
Risk /100 (95% CI)	12.4 (11.0, 13.9)	13.8 (12.0, 15.6)	14.2 (12.0, 16.4)	13.6 (11.2, 15.9)
Stratified RD /100 (95% CI)	−1.4 (−3.5, 0.8)	Ref	0.6 (−2.5, 3.8)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	1.1 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−1.1 (−3.9, 1.6)	0.2 (−2.7, 3.1)	0.6 (−2.5, 3.8)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	Ref
12 months				
Risk /100 (95% CI)	15.1 (13.4, 16.8)	15.5 (13.4, 17.7)	17.8 (15.2, 20.4)	17.6 (14.4, 20.8)
Stratified RD /100 (95% CI)	−0.4 (−2.9, 2.0)	Ref	0.2 (−4.0, 4.4)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	1.0 (0.8, 1.3)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.1, 0.9)	−2.1 (−5.9, 1.6)	0.2 (−4.0, 4.4)	Ref
Common Ref RR (95% CI)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	Ref
Leukopenia				
High Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	11.5 (10.2, 12.9)	11.7 (9.9, 13.4)	8.4 (6.9, 9.8)	8.0 (6.1, 9.9)
Stratified RD /100 (95% CI)	−0.1 (−2.2, 2.0)	Ref	0.3 (−2.0, 2.7)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.7, 1.4)	Ref
Common Ref RD /100 (95% CI)	3.5 (1.3, 5.8)	3.6 (1.0, 6.3)	0.3 (−2.0, 2.7)	Ref
Common Ref RR (95% CI)	1.5 (1.1, 1.9)	1.5 (1.0, 1.9)	1.1 (0.7, 1.4)	Ref
6 months				
Risk /100 (95% CI)	15.0 (13.6, 16.5)	13.0 (11.1, 14.9)	11.8 (10.0, 13.7)	9.8 (7.7, 11.9)
Stratified RD /100 (95% CI)	2.0 (−0.3, 4.4)	Ref	2.0 (−0.7, 4.8)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.4)	Ref	1.2 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	5.2 (2.7, 7.7)	3.2 (0.3, 6.0)	2.0 (−0.7, 4.8)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	17.9 (16.2, 19.6)	14.4 (12.2, 16.6)	16.2 (13.8, 18.6)	11.5 (9.1, 14.0)

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Stratified RD /100 (95% CI)	3.5 (0.7, 6.3)	Ref	4.7 (1.1, 8.3)	Ref
Stratified RR (95% CI)	1.3 (1.0, 1.5)	Ref	1.4 (1.0, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.4 (3.5, 9.3)	2.9 (−0.3, 6.1)	4.7 (1.1, 8.3)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (0.9, 1.6)	1.4 (1.0, 1.8)	Ref
Standard Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	11.5 (10.2, 12.9)	11.7 (9.9, 13.4)	8.4 (6.9, 9.8)	8.0 (6.1, 9.9)
Stratified RD /100 (95% CI)	−0.1 (−2.2, 2.0)	Ref	0.3 (−2.0, 2.7)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.7, 1.4)	Ref
Common Ref RD /100 (95% CI)	3.5 (1.3, 5.8)	3.6 (1.0, 6.3)	0.3 (−2.0, 2.7)	Ref
Common Ref RR (95% CI)	1.5 (1.1, 1.9)	1.5 (1.0, 1.9)	1.1 (0.7, 1.4)	Ref
6 months				
Risk /100 (95% CI)	15.0 (13.6, 16.5)	13.0 (11.1, 14.9)	11.8 (10.0, 13.7)	9.8 (7.7, 11.9)
Stratified RD /100 (95% CI)	2.0 (−0.3, 4.4)	Ref	2.0 (−0.7, 4.8)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.4)	Ref	1.2 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	5.2 (2.7, 7.7)	3.2 (0.3, 6.0)	2.0 (−0.7, 4.8)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	17.9 (16.2, 19.6)	14.4 (12.2, 16.6)	16.2 (13.8, 18.6)	11.5 (9.1, 14.0)
Stratified RD /100 (95% CI)	3.5 (0.7, 6.3)	Ref	4.7 (1.1, 8.3)	Ref
Stratified RR (95% CI)	1.3 (1.0, 1.5)	Ref	1.4 (1.0, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.4 (3.5, 9.3)	2.9 (−0.3, 6.1)	4.7 (1.1, 8.3)	Ref
Common Ref RR (95% CI)	1.6 (1.2, 1.9)	1.3 (0.9, 1.6)	1.4 (1.0, 1.8)	Ref
Neutropenia				
High Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	12.5 (11.1, 13.8)	10.3 (8.6, 12.0)	8.2 (6.6, 9.9)	6.4 (4.7, 8.1)
Stratified RD /100 (95% CI)	2.2 (−0.1, 4.4)	Ref	1.8 (−0.6, 4.2)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.5)	Ref	1.3 (0.9, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.1 (4.0, 8.1)	3.9 (1.4, 6.3)	1.8 (−0.6, 4.2)	Ref
Common Ref RR (95% CI)	2.0 (1.4, 2.5)	1.6 (1.1, 2.2)	1.3 (0.9, 1.8)	Ref
6 months				
Risk /100 (95% CI)	17.0 (15.4, 18.6)	12.1 (10.3, 14.0)	13.6 (11.4, 15.8)	8.2 (6.3, 10.1)
Stratified RD /100 (95% CI)	4.9 (2.4, 7.4)	Ref	5.4 (2.4, 8.4)	Ref
Stratified RR (95% CI)	1.4 (1.2, 1.7)	Ref	1.7 (1.2, 2.2)	Ref
Common Ref RD /100 (95% CI)	8.8 (6.4, 11.3)	4.0 (1.4, 6.5)	5.4 (2.4, 8.4)	Ref
Common Ref RR (95% CI)	2.1 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.2, 2.2)	Ref
12 months				
Risk /100 (95% CI)	22.6 (20.6, 24.6)	15.3 (12.8, 17.7)	18.1 (15.7, 20.6)	10.6 (8.2, 13.0)
Stratified RD /100 (95% CI)	7.4 (4.2, 10.5)	Ref	7.5 (4.3, 10.8)	Ref
Stratified RR (95% CI)	1.5 (1.2, 1.8)	Ref	1.7 (1.3, 2.2)	Ref
Common Ref RD /100 (95% CI)	12.0 (9.0, 15.1)	4.7 (1.3, 8.1)	7.5 (4.3, 10.8)	Ref
Common Ref RR (95% CI)	2.2 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	Ref
Standard Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	12.5 (11.1, 13.8)	10.3 (8.6, 12.0)	8.2 (6.6, 9.9)	6.4 (4.7, 8.1)
Stratified RD /100 (95% CI)	2.2 (−0.1, 4.4)	Ref	1.8 (−0.6, 4.2)	Ref
Stratified RR (95% CI)	1.2 (1.0, 1.5)	Ref	1.3 (0.9, 1.8)	Ref
Common Ref RD /100 (95% CI)	6.1 (4.0, 8.1)	3.9 (1.4, 6.3)	1.8 (−0.6, 4.2)	Ref
Common Ref RR (95% CI)	2.0 (1.4, 2.5)	1.6 (1.1, 2.2)	1.3 (0.9, 1.8)	Ref
6 months				
Risk /100 (95% CI)	17.0 (15.4, 18.6)	12.1 (10.3, 14.0)	13.6 (11.4, 15.8)	8.2 (6.3, 10.1)
Stratified RD /100 (95% CI)	4.9 (2.4, 7.4)	Ref	5.4 (2.4, 8.4)	Ref
Stratified RR (95% CI)	1.4 (1.2, 1.7)	Ref	1.7 (1.2, 2.2)	Ref
Common Ref RD /100 (95% CI)	8.8 (6.4, 11.3)	4.0 (1.4, 6.5)	5.4 (2.4, 8.4)	Ref
Common Ref RR (95% CI)	2.1 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.2, 2.2)	Ref
12 months				
Risk /100 (95% CI)	22.6 (20.6, 24.6)	15.3 (12.8, 17.7)	18.1 (15.7, 20.6)	10.6 (8.2, 13.0)
Stratified RD /100 (95% CI)	7.4 (4.2, 10.5)	Ref	7.5 (4.3, 10.8)	Ref
Stratified RR (95% CI)	1.5 (1.2, 1.8)	Ref	1.7 (1.3, 2.2)	Ref
Common Ref RD /100 (95% CI)	12.0 (9.0, 15.1)	4.7 (1.3, 8.1)	7.5 (4.3, 10.8)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	**Not Exposed to IMiDs during LOT 2**	**Exposed to IMiDs during LOT 2**	**Not Exposed to IMiDs during LOT 2**
Common Ref RR (95% CI)	2.2 (1.6, 2.7)	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	Ref
Lymphocytopenia				
High Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	20.8 (19.2, 22.5)	23.0 (20.7, 25.3)	21.4 (19.0, 23.8)	23.4 (20.5, 26.3)
Stratified RD /100 (95% CI)	−2.1 (−5.1, 0.8)	Ref	−2.0 (−5.7, 1.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.0)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.0, 0.8)	−0.4 (−4.3, 3.4)	−2.0 (−5.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	Ref
6 months				
Risk /100 (95% CI)	25.9 (23.9, 27.8)	27.5 (24.7, 30.2)	25.5 (22.8, 28.1)	27.5 (24.3, 30.6)
Stratified RD /100 (95% CI)	−1.6 (−5.1, 1.9)	Ref	−2.0 (−5.9, 1.9)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−5.3, 2.1)	0.0 (−4.4, 4.4)	−2.0 (−5.9, 1.9)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	Ref
12 months				
Risk /100 (95% CI)	29.9 (27.8, 32.0)	30.8 (27.6, 34.1)	29.5 (26.5, 32.5)	32.7 (28.9, 36.5)
Stratified RD /100 (95% CI)	−0.9 (−5.0, 3.1)	Ref	−3.2 (−8.0, 1.6)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.8, 1.0)	Ref
Common Ref RD /100 (95% CI)	−2.8 (−7.2, 1.6)	−1.9 (−7.0, 3.2)	−3.2 (−8.0, 1.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	Ref
Standard Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	20.8 (19.2, 22.5)	23.0 (20.7, 25.3)	21.4 (19.0, 23.8)	23.4 (20.5, 26.3)
Stratified RD /100 (95% CI)	−2.1 (−5.1, 0.8)	Ref	−2.0 (−5.7, 1.7)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.0)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−2.6 (−6.0, 0.8)	−0.4 (−4.3, 3.4)	−2.0 (−5.7, 1.7)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	Ref
6 months				
Risk /100 (95% CI)	25.9 (23.9, 27.8)	27.5 (24.7, 30.2)	25.5 (22.8, 28.1)	27.5 (24.3, 30.6)
Stratified RD /100 (95% CI)	−1.6 (−5.1, 1.9)	Ref	−2.0 (−5.9, 1.9)	Ref
Stratified RR (95% CI)	0.9 (0.8, 1.1)	Ref	0.9 (0.8, 1.1)	Ref
Common Ref RD /100 (95% CI)	−1.6 (−5.3, 2.1)	0.0 (−4.4, 4.4)	−2.0 (−5.9, 1.9)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	Ref
12 months				
Risk /100 (95% CI)	29.9 (27.8, 32.0)	30.8 (27.6, 34.1)	29.5 (26.5, 32.5)	32.7 (28.9, 36.5)
Stratified RD /100 (95% CI)	−0.9 (−5.0, 3.1)	Ref	−3.2 (−8.0, 1.6)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.1)	Ref	0.9 (0.8, 1.0)	Ref
Common Ref RD /100 (95% CI)	−2.8 (−7.2, 1.6)	−1.9 (−7.0, 3.2)	−3.2 (−8.0, 1.6)	Ref
Common Ref RR (95% CI)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	Ref
Thrombocytopenia				
High Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	7.4 (6.3, 8.4)	12.8 (10.9, 14.7)	7.4 (5.7, 9.0)	7.5 (5.7, 9.3)
Stratified RD /100 (95% CI)	−5.5 (−7.5, −3.4)	Ref	−0.1 (−2.5, 2.2)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.7)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	−0.1 (−2.2, 2.0)	5.3 (2.6, 8.0)	−0.1 (−2.5, 2.2)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.3)	1.7 (1.2, 2.2)	1.0 (0.7, 1.3)	Ref
6 months				
Risk /100 (95% CI)	10.5 (9.0, 11.9)	14.3 (12.2, 16.4)	11.4 (9.2, 13.6)	9.2 (7.1, 11.3)
Stratified RD /100 (95% CI)	−3.8 (−6.3, −1.3)	Ref	2.2 (−0.8, 5.1)	Ref
Stratified RR (95% CI)	0.7 (0.6, 0.9)	Ref	1.3 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.3 (−1.3, 3.9)	5.1 (2.0, 8.2)	2.2 (−0.8, 5.1)	Ref
Common Ref RR (95% CI)	1.2 (0.8, 1.5)	1.6 (1.1, 2.0)	1.3 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	12.9 (11.4, 14.5)	15.4 (13.2, 17.6)	15.5 (9.0, 21.9)	10.8 (8.6, 13.0)
Stratified RD /100 (95% CI)	−2.5 (−5.1, 0.2)	Ref	4.6 (−2.1, 11.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.4 (0.8, 2.1)	Ref
Common Ref RD /100 (95% CI)	2.1 (−0.6, 4.8)	4.6 (1.4, 7.8)	4.6 (−2.1, 11.4)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.4 (1.1, 1.8)	1.4 (0.8, 2.1)	Ref

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
Standard Cytogenetic Risk				
3 months				
Risk /100 (95% CI)	7.4 (6.3, 8.4)	12.8 (10.9, 14.7)	7.4 (5.7, 9.0)	7.5 (5.7, 9.3)
Stratified RD /100 (95% CI)	−5.5 (−7.5, −3.4)	Ref	−0.1 (−2.5, 2.2)	Ref
Stratified RR (95% CI)	0.6 (0.5, 0.7)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	−0.1 (−2.2, 2.0)	5.3 (2.6, 8.0)	−0.1 (−2.5, 2.2)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.3)	1.7 (1.2, 2.2)	1.0 (0.7, 1.3)	Ref
6 months				
Risk /100 (95% CI)	10.5 (9.0, 11.9)	14.3 (12.2, 16.4)	11.4 (9.2, 13.6)	9.2 (7.1, 11.3)
Stratified RD /100 (95% CI)	−3.8 (−6.3, −1.3)	Ref	2.2 (−0.8, 5.1)	Ref
Stratified RR (95% CI)	0.7 (0.6, 0.9)	Ref	1.3 (0.9, 1.6)	Ref
Common Ref RD /100 (95% CI)	1.3 (−1.3, 3.9)	5.1 (2.0, 8.2)	2.2 (−0.8, 5.1)	Ref
Common Ref RR (95% CI)	1.2 (0.8, 1.5)	1.6 (1.1, 2.0)	1.3 (0.9, 1.6)	Ref
12 months				
Risk /100 (95% CI)	12.9 (11.4, 14.5)	15.4 (13.2, 17.6)	15.5 (9.0, 21.9)	10.8 (8.6, 13.0)
Stratified RD /100 (95% CI)	−2.5 (−5.1, 0.2)	Ref	4.6 (−2.1, 11.4)	Ref
Stratified RR (95% CI)	0.8 (0.7, 1.0)	Ref	1.4 (0.8, 2.1)	Ref
Common Ref RD /100 (95% CI)	2.1 (−0.6, 4.8)	4.6 (1.4, 7.8)	4.6 (−2.1, 11.4)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.4 (1.1, 1.8)	1.4 (0.8, 2.1)	Ref

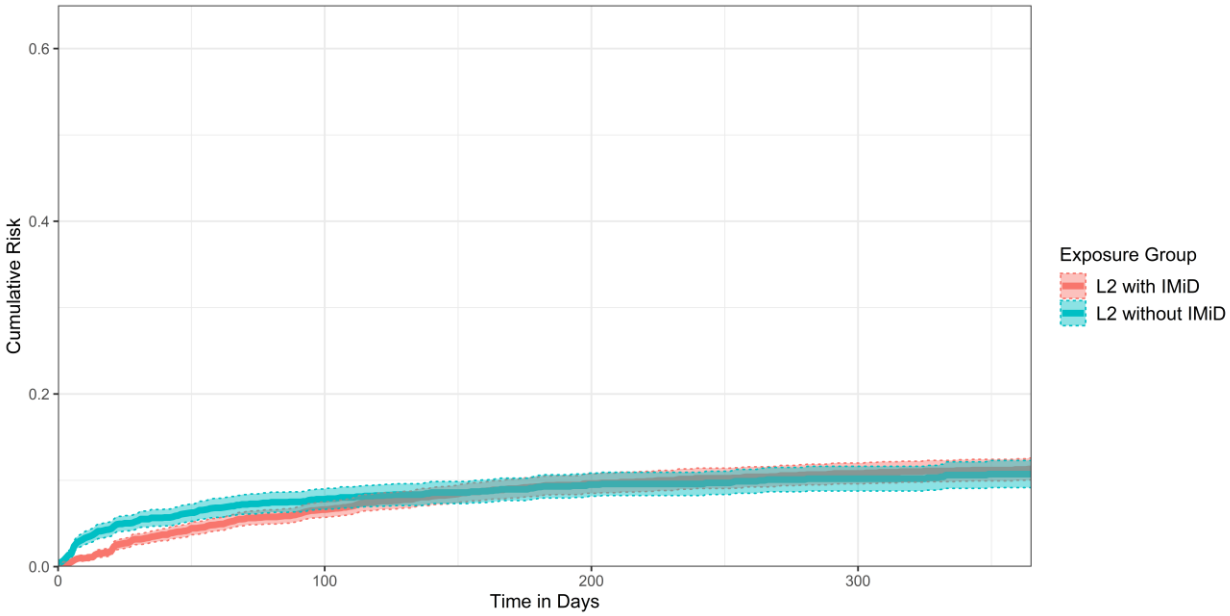
Exploratory Analysis

G-CSF initiation occurred on the index date (second LOT start date) for 26 patients, who were therefore excluded from this analysis. The incidence of G-CSF prescribing following initiation of the second LOT was similar among those exposed, versus unexposed, to IMiDs across the entirety of follow-up (3 months 6.1% versus 7.5%, 6 months 9.3% versus 9.2%, 12 months 11.3% versus 10.7%) (**Table 29** and **Figure 26**).

Table 29. Risks per 100, risk differences per 100, and risk ratios of G-CSF prescribing following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs

	Exposed to IMiDs during LOT 2 Risk /100 (95% CI)	Not Exposed to IMiDs during LOT 2 Risk /100 (95% CI)	Risk Difference /100 (95% CI)	Risk Ratio (95% CI)
3 months	6.1 (5.2, 6.9)	7.5 (6.3, 8.7)	-1.4 (-2.8, 0.0)	0.8 (0.7, 1.0)
6 months	9.3 (8.2, 10.4)	9.2 (7.9, 10.6)	0.0 (-1.6, 1.7)	1.0 (0.8, 1.2)
12 months	11.3 (10.0, 12.6)	10.7 (9.2, 12.3)	0.6 (-1.4, 2.5)	1.1 (0.9, 1.2)

Figure 26. Cumulative incidence of G-CSF prescribing following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy



Stratification on prior IMiD exposure did not meaningfully change the incidence of G-CSF prescribing (**Table 30** and **Figure 27**).

Figure 27. Cumulative incidence of G-CSF prescribing following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs during the second line of therapy, stratified by exposure during the first line of therapy

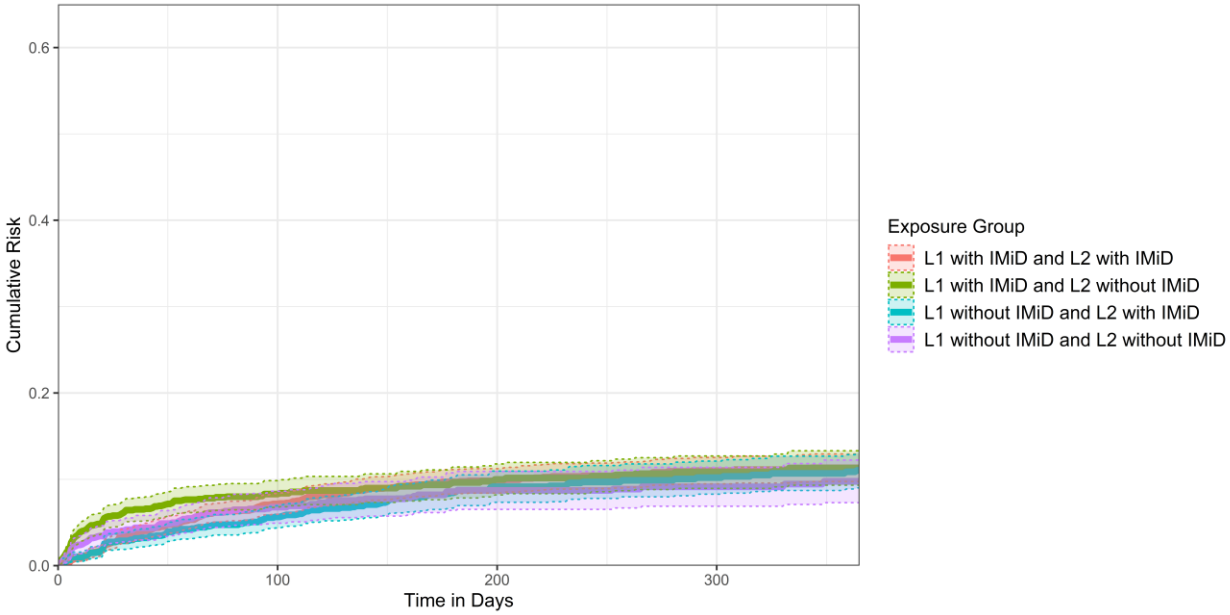


Table 30. Risks per 100, risk differences per 100, and risk ratios of G-CSF prescribing following second line of therapy initiation in those exposed versus unexposed to immunomodulatory drugs, stratified by first line of therapy exposure

	Exposed to IMiDs during LOT 1		Not Exposed to IMiDs during LOT 1	
	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2	Exposed to IMiDs during LOT 2	Not Exposed to IMiDs during LOT 2
3 months				
Risk /100 (95% CI)	6.7 (5.5, 7.8)	8.0 (6.5, 9.5)	5.1 (3.8, 6.3)	6.6 (4.8, 8.4)
Stratified RD /100 (95% CI)	-1.3 (-3.2, 0.6)	Ref	-1.5 (-3.6, 0.6)	Ref
Stratified RR (95% CI)	0.8 (0.6, 1.1)	Ref	0.8 (0.5, 1.1)	Ref
Common Ref RD /100 (95% CI)	0.1 (-1.9, 2.1)	1.4 (-1.0, 3.9)	-1.5 (-3.6, 0.6)	Ref
Common Ref RR (95% CI)	1.0 (0.7, 1.4)	1.2 (0.8, 1.7)	0.8 (0.5, 1.1)	Ref
6 months				
Risk /100 (95% CI)	9.7 (8.3, 11.1)	9.6 (7.8, 11.4)	8.4 (6.7, 10.2)	8.6 (6.4, 10.7)
Stratified RD /100 (95% CI)	0.1 (-2.1, 2.2)	Ref	-0.1 (-2.7, 2.5)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.0 (0.7, 1.3)	Ref
Common Ref RD /100 (95% CI)	1.1 (-1.4, 3.6)	1.1 (-1.9, 4.0)	-0.1 (-2.7, 2.5)	Ref
Common Ref RR (95% CI)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	Ref
12 months				
Risk /100 (95% CI)	11.3 (9.7, 12.9)	11.3 (9.3, 13.3)	11.0 (9.0, 13.0)	9.8 (7.3, 12.2)
Stratified RD /100 (95% CI)	0.0 (-2.5, 2.5)	Ref	1.3 (-1.7, 4.3)	Ref
Stratified RR (95% CI)	1.0 (0.8, 1.2)	Ref	1.1 (0.8, 1.5)	Ref
Common Ref RD /100 (95% CI)	1.6 (-1.2, 4.3)	1.6 (-1.7, 4.8)	1.3 (-1.7, 4.3)	Ref
Common Ref RR (95% CI)	1.2 (0.9, 1.5)	1.2 (0.8, 1.5)	1.1 (0.8, 1.5)	Ref

Discussion

Overall, exposure to IMiDs during the second LOT, compared with no iMiD in the second LOT, increased the risk of severe leukopenia and neutropenia, but not anemia, lymphocytopenia, and thrombocytopenia. It appears that the association with leukopenia (which is based on counts of total white blood cells) may be driven by neutrophil counts, rather than other types of white blood cells (e.g., lymphocytes), given the observed association for neutropenia yet not for lymphocytopenia. Proposed biologic mechanisms in the literature are consistent with these results, as IMiDs have been linked with disruption of blood cell development processes specific to granulocytes (which give rise to neutrophils), yet not to those that give rise to lymphocytes.[130-132] No strong evidence of biologic mechanisms relating IMiDs to development of red blood cells or platelets has been published, perhaps supporting why we did not observe treatment-related differences for the risks of cytopenias related to these blood cell types.[133, 134]

Results also suggest sequential exposure to IMiDs across two LOTs to be mainly of concern for

risk of severe cytopenias related to white blood cells, especially neutrophils, given the observed trends in the common referent relative risks for leukopenia and neutropenia only. The specificity of this finding to this type of white blood cell, as described above, is supported by biological mechanisms related to IMiD suppression of neutrophil production.[130-132] The mechanism by which first LOT IMiD exposure may impact post-second LOT neutrophil production, independent of its effect on post-first LOT neutrophil production, is not clear as previous studies, to our knowledge, have not described neutropenia risks associated with sequential IMiD exposure. A pharmacologic study using a mouse model to inhibit the transcription factors involved in the IMiD-associated granulocytes development pathway found the effects to be reversible following removal of the inhibitor, with no evidence of long-term impairment; the impact of IMiD removal and re-treatment in MM patients, however, has not been examined.[132]

For all cytopenias under study, the risks were substantially higher among those with, compared to without, a recent history. We expect this to be indicative of an underlying propensity for the myelosuppression, rather than a continuation of the previously experienced low blood cell counts, given the acuteness of cytopenia episodes (i.e., due to corrections with dosing and regimen adjustments, which are expected to recover blood counts within one month), evidenced in our study by the observation that only a subset of patients with cytopenias during the first LOT had cytopenias during the second LOT as well.[135, 143, 188-192] However, future research, perhaps in an experimental setting in which regimented blood testing at regular intervals is possible, should examine blood count trajectories through the treatment course for MM patients. Results suggest sequential exposure to IMiDs across two LOTs to be associated with a heightened risk of severe cytopenias related to white blood cells, especially neutrophils, for those who have a recent history of these blood cell deficiencies. Given the observation that the risks of cytopenias not related to white blood cells (anemia, thrombocytopenia) among those with no recent history were low (<10%), even for those sequentially exposed, it does not appear

that prescribing choices at the second line of therapy need be concerned with whether the choice to administer an IMiD will impact risks of these cytopenias for those without a history.

We also explored the impact on the resulting relative risks of stratifying on patient age (75+ versus <75) and cytogenetic risk at baseline. We did not find stratification on patient age category to notably alter the cumulative risks or relative risks of any of the cytopenias under study for those exposed, versus unexposed, to IMiDs during the first and/or second LOTs. Patient age is a known risk factor for cytopenia, so we had expected to observe at least heightened cumulative risks of each cytopenia in the age 75+ strata.[143] However, perhaps this binary stratification is not meaningful and instead a differential risk would have been observed at an alternative categorization. In any case, results suggest that clinicians need not have special concern with prescribing sequential IMiDs on the risk of white blood cell cytopenias, especially neutropenia, for older versus younger adults independently of cytopenia history. We also did not find stratification on cytogenetic risk at baseline to alter the cumulative risks or relative risks of any of the cytopenias under study for those exposed, versus unexposed, to IMiDs during the first and/or second LOTs. This suggests, similarly to age, that baseline cytogenetic risk (which is generally used as a tool for disease prognosis prediction, not necessarily for hematologic adverse event prediction) does not alter the IMiD-cytopenia relationship and therefore may not need to be a consideration when deciding whether it is safe to prescribe a sequential IMiD treatment in terms of cytopenia risk.[159]

Despite the associations observed for risks of severe neutropenia following second LOT initiation among those with varying first and second LOT IMiD exposure, no meaningful differences in the prescribing of G-CSF were observed. Given that G-CSF is used to counteract neutropenia by stimulating neutrophil production, we had expected the cumulative incidence of G-CSF prescribing to mimic the patterns observed for severe neutropenia incidence.[186, 187] Treatment-related cytopenia episodes are addressed via interruptions in the treatment regimen

or reductions in treatment dosage to allow for recovery of blood cell counts back to normal levels.[143, 188] G-CSF support is often a recommended treatment only after the failure of dose delays or reductions alone to recover neutrophil levels.[143, 188] Randomized clinical trials involving IMiD treatment arms have reported that dose reductions and delays due to neutropenia may occur in 4–7% and 9–23% of MM patients, respectively.[146, 147] Unfortunately, we were unable to examine dose reductions and delays as endpoints in our analysis due to the limitations of the data available in the Flatiron database. It is possible that patients exposed, versus unexposed, to IMiDs have their excess neutropenia incidence addressed via dose changes, such that the remaining patients needing the extra support of G-CSF are a similar proportion to those also requiring this support in the unexposed group.

This analysis is not without limitations. First, as the Flatiron database compiles EHR data from oncology clinics only, diagnoses and blood draws occurring in other settings will be under-recorded. In addition to having implications on the ascertainment of our study outcomes (as well as observed rates of G-CSF prescribing in the exploratory analysis), the under-reporting of diagnoses and laboratory results from other settings hinders our ability to examine additional, clinically relevant safety endpoints that are important consequences of cytopenias, such as hospitalizations and infections. We expect, however, the diagnoses, medication administrations, and laboratory tests that occurred in the oncology clinic setting to be well-captured and highly accurate. Additionally, as our study population constituted cancer patients of advanced age receiving active therapy, it is unlikely for patients to be attending alternative care facilities for their cancer treatment and therefore we expect the Flatiron database to offer a complete picture of the disease-related variables under study.

Next, the Flatiron database was also subject to additional limitations in terms of the availability and completeness of covariate data. There were additional potential confounders of the IMiD-cytopenia associations that we would have liked to control for, such as bone lytic lesions or

bone marrow plasma counts, which are unavailable in the Flatiron database. As a result, there is a possibility of at least some residual confounding due to these unmeasured confounders. For the confounding variables that were available in the Flatiron database, some were subject to missingness. For example, between 10–30% of patients were missing one of the baseline blood component level tests and around 40% of patients did not have a record of MM clinical characteristics (i.e., ECOG score, ISS, cytogenetics). This level of missingness is similar to that observed in clinical trials; pooled analyses of MM clinical trials have reported missingness for cytogenetics and ISS to be around 15–25%.[193, 194] In our analyses, missing confounder information was addressed using multiple imputation. Although this method could result in some confounder misclassification, it is generally less biased than other missing data methods (e.g., complete case analysis, missing indicator method).[195] Multiple imputation was implemented under the assumption that the data were missing at random, such that the reason for missingness is independent of the values themselves, conditional on the measured covariates. It is possible that this assumption could have been violated, as it has been suggested that missingness of clinical characteristics in electronic health records databases may be due to an unrecorded determination by the physician that the patient is unlikely to be at risk of that covariate.[196] We do expect, however, that conditional on the values of the observed covariates, the missingness is unlikely to be dependent on the missing values themselves (e.g., a blood test to detect cytopenias may only be ordered for patients considered likely to have cytopenia, which may be defined by the set of their measured characteristics such as age, treatment history, performance status).[197]

Given that the cytopenia outcomes were defined using blood tests, there is some concern regarding potential outcome misclassification. Although care for MM patients is typically regimented to involve regular follow-up, it is possible for the timing and frequency of laboratory tests to vary at the clinic, physician, or patient level. Furthermore, certain bloodwork may not be

conducted on a schedule (as it would in a clinical trial), and rather may occur in response to certain patient symptoms or other factors. If patients with symptoms are more likely to visit the clinic and have blood testing performed, they may be more likely to have the cytopenia outcome observed (i.e., informative presence[198]). This informative presence bias may result in imperfect sensitivity of the cytopenia outcome (i.e., some individuals with cytopenia may not have their outcome observed). Furthermore, IMiD versus non-IMiD exposure status may be associated with testing frequency, given that treatment guidelines do advise monitoring blood component levels for patients receiving IMiDs, causing the outcome misclassification to potentially be differential with respect to the exposure.[135, 148] In particular, weekly blood component testing is recommended for the first eight weeks of IMiD treatment, and monthly thereafter.[135, 148] However, because treatment guidelines do suggest assessing complete blood counts monthly for all MM patients, blood component testing may occur at similar frequencies between patients receiving and not receiving IMiDs beyond the first two months after treatment initiation.[199] In any case, we do expect that patients without cytopenia would be unlikely to be recorded as having cytopenia (i.e., specificity of the outcome is expected to be perfect or nearly perfect). We therefore expect the cytopenia outcome events in this cohort to be under-captured, as a result of the imperfect sensitivity and perfect specificity. Compared to neutropenia risks among MM patients treated with IMiDs in randomized clinical trials (40–60%), the neutropenia risks observed in our analysis (10–20%, except among those with a recent neutropenia history, for which the risks were 25–40%) do support an underestimation of the cytopenia outcomes in this population.[139, 140, 144-148] In the present analyses, patients were censored upon loss to follow-up, which was defined as greater than 30 days after the last clinical encounter, which we expect to have diminished the number of patients missing a recorded blood test during the follow-up period. Inverse probability of censoring weights were used to account for potentially differential rates of loss to follow-up, for example if those receiving IMIDs were more likely to be kept under more regular care than those on non-IMiD regimens.[135, 148] Future studies may further explore

the presence and timing of blood component tests during the follow-up period, stratified by IMiD exposure status, to understand the potential for bias due to differential misclassification of the outcome. Should differential testing rates be supported by the data, potential use of inverse probability weighting may help to reduce bias due to non-random blood component testing in future studies with this cohort.[200]

This analysis is also limited by missingness of the exact date of death. Date of death is only reported at the granularity of month and year in the Flatiron database for de-identification purposes. The fifteenth day of the month was therefore imputed as the estimated date of death. This is the method suggested by Flatiron to best approximate the actual death date. We acknowledge, however, that this could have resulted in potential misclassification of the death date, which may have altered follow-up time (resulting in either counting of additional follow-up time beyond patient death or premature stopping of follow-up time before the patient has died). We do not expect, however, this misclassification to be related to either the exposure or the outcome.

Next, in the present analysis, we observed that 10–60% of MM patients experienced one of the cytopenias of interest during the first LOT, prior to the index date. We assumed the prior experience of cytopenias to be an indicator of a predisposition for future myelosuppression and a consideration for second LOT prescribing and therefore treated these variables as confounders, and explored as effect modifiers, in our analyses. We further assumed that the experience of cytopenias during the first LOT would be an acute event that would have been resolved before the initiation of the second, therefore qualifying the experience of cytopenias during the second LOT as incident episodes of the outcome.[143, 188, 201] Randomized clinical trials of MM patients treated with IMiDs have reported dose interruptions and reductions associated with any adverse event to occur, respectively, for 66–73% and 22–59% of patients.[139, 140, 144-147, 150] Although less often described in the clinical trial literature, dose interruptions in response to

cytopenias specifically have been reported to occur for 5–23% of patients, while dose reductions in response to cytopenias occurred for only 4–9% of patients.[146, 147] G-CSF prescribing in response to IMiD-associated neutropenia incidence has been reported in 22–58% of MM patients.[128, 139, 140, 145, 147] With these actions, blood counts are expected to be restored within one month, with rapid resolution of neutropenia within one week expected with receipt of G-CSF.[135, 190-192, 202] It is possible, however, that first LOT cytopenias could have failed to resolve, which would make the observed occurrence of cytopenias during the second LOT a continuation of the previous episode, rather than an incident event. If physicians are aware that a patient is experiencing a cytopenia episode at the time of second LOT prescribing, they may be more likely to prescribe a non-IMiD regimen given the known myelosuppressive effects of IMiDs. This would result in an artificially inflated rate of cytopenias in those unexposed to IMiDs during the second LOT and would therefore likely bias any IMiD-associated cytopenia relative risk towards the null. However, we do expect this to occur rarely, if ever, given that physicians would likely be testing blood counts and delaying treatment start were a patient to exhibit active cytopenia. Reassuringly, our stratified analyses based on recent cytopenia histories allowed us to examine the associations between receipt of IMiDs and risks of cytopenias in a population restricted to those with incident cytopenias post-second LOT. There were no differences in the relative risks among the strata with no recent cytopenia history compared with the main analyses.

Another potential threat to validity is channeling bias (a type of confounding).[203] It is of concern that physicians may use prognostic characteristics to make decisions regarding second line (and subsequent) treatment for relapsed MM patients (e.g., age, ECOG performance status, comorbidities, history of treatment response[123]), in which case specific regimens may be channeled to, and others withheld from, patients at a heightened risk for cytopenia. Data on important prognostic characteristics that may bias second line treatment decisions were

available and were used to create inverse probability weights. Additionally, year of availability of the various drug combinations could result in selective prescribing, such that patients with increasing disease severity and at an increased cytopenia risk could be preferentially prescribed newer drug combinations.[204] For this reason, year of MM diagnosis was included in the treatment model to address this type of confounding. Finally, it is possible that the treatment center where care was received could be an important determinant of treatment choice and a proxy for socioeconomic cytopenia risk factors. For this reason, sensitivity analyses were performed in which patients were clustered within treatment centers. The results of these multilevel models were not different from those of the main analyses. It is possible that inclusion of practice type (academic versus community) in our treatment models may have adequately addressed variation in treatment-related cytopenia risk due to features of the healthcare system, and therefore the additional clustering within treatment center did not alter results. Future work may examine the impact of the healthcare system, at the level of the treatment center as well as the physician, on prescribing patterns and cytopenia risks in MM patients.

This analysis is also limited by a lack of flexibility in the definitions of the LOT variables, which are pre-defined by Flatiron. However, given that the complex algorithm used to define each component of LOT (e.g., start date, end date, name) was developed by a team of clinical experts, we expect these features to be well-classified and clinically relevant. Although a validation study using data on 100 MM patients through September 2017 found suboptimal agreement of Flatiron-algorithm-defined versus clinician-defined LOT variables (81% agreement for first LOT, 43% agreement for second LOT), several components of the Flatiron algorithm have been implemented and/or amended since then and therefore validity is expected to be improved.[205] Use of the Flatiron pre-defined variables, despite possible misclassification, is preferable over re-defining the LOT variables using our own algorithm as it will facilitate comparability with other studies conducted in this database in the literature.

We considered two features of the Flatiron LOT algorithm to assess the impact of the inflexibility of the LOT variables. First, although the Flatiron algorithm allows the start date of the first LOT to occur up to 14 days before MM diagnosis (to allow for delayed entry of the diagnosis in the EHR), clinical guidance has suggested that delayed entry is quite common and, in some cases, may be as long as 28 days. For this reason, we examined the distribution of time between MM diagnosis and first LOT start date for evidence of tapering off as the number of days before MM diagnosis increases, which would provide evidence that we do not need to be concerned about missing a large proportion of MM patients whose first LOT begins more than 14 days before their recorded MM diagnosis. This analysis revealed that >90% of MM patients started their first LOT on or up to 90 days after their diagnosis date, with 6.5% of patients initiating their first LOT after 90 days but within one year of their diagnosis date and 2% initiating a year or more after their diagnosis date. The remaining <1.5% (N = 66) of patients had their first LOT start date recorded up to 14 days before their diagnosis date. There was no evidence of a decrease in patients with LOT start days as the number of days before MM diagnosis increased; the number of patients starting the first LOT was evenly distributed from one up to 14 days before diagnosis. It is therefore possible that extending the pre-diagnosis first LOT start window up to 28 days could have identified additional eligible patients of similar magnitude as the 0- to 14-day window. Instead, however, these patients would have their first drug episode the occurred within the eligible window counted as their first LOT start date, therefore shifting the recorded start date later in time relative to the true start date. This would result in an artificially shorter time to cytopenia incidence in these patients. Given that we do not anticipate this potential issue to impact a large number of patients, and do not expect the recording of the first LOT initiation relative to the diagnosis date to be differential with respect to the IMiD exposure or the cytopenia outcomes, we are not concerned about potential bias in this circumstance.

Next, Flatiron names the LOT based on all drugs received within 28 days of the start of the LOT.

Clinical guidance has suggested extending this another week to allow for variability in the scheduling of patient follow-up visits (at which point regimen adjustments would occur) and delayed entry of medications in the EHR. Certain changes are allowed beyond 28 days, but do not update the LOT name. For example, the addition of an IMiD to a regimen that did not previously contain an IMiD within 90 days of the LOT start does not advance the LOT number and does not result in an updated LOT name. Similarly, de-escalation of a regimen (e.g., from a triplet to a doublet) beyond 28 days after the start of the LOT is also considered to be the same LOT, so does not update the LOT name. It is therefore theoretically possible that patients who begin on an IMiD-containing regimen could have their IMiD removed. Given these scenarios, it is possible that some patients could be labeled as using a non-IMiD regimen, yet be taking an IMiD (imperfect sensitivity), while others may be labeled as taking an IMiD regimen, yet not being taking an IMiD (imperfect specificity). The impact of this potential exposure misclassification is unknown, but could potentially be differential with respect to the outcome given that patients who are at an increased risk of cytopenias may be more likely to have their regimen altered. However, there would be no bias if regimen changes of this nature were to occur in direct response to a cytopenia diagnosis, as the regimen as recorded before the change would be reflective of the patient's true exposure.

This analysis may also suffer from violations of counterfactual model sequential consistency.[206] Within the IMiD exposure group, an individual may be exposed to lenalidomide, pomalidomide, or thalidomide, each of which may be associated with a different risk of developing cytopenias. For example, neutropenia is a common adverse event associated with both lenalidomide and pomalidomide, affecting as many as 60% of MM patients.[128, 129, 135-148] In contrast, neutropenia does not appear to be a common side effect of thalidomide, affecting less than 10% of MM patients.[149, 150] Exposure to thalidomide was low in this cohort (less than 3%), which likely reduces the impact of outcome variance among the IMiD-exposed due to the receipt of

thalidomide versus lenalidomide or pomalidomide. In addition to the receipt of different IMiDs drugs, patients may also receive different doses of these drugs, in different combinations with other drug classes, which may also contribute to differential cytopenia risk.[187] There may also be treatment-related outcome variance among those unexposed to IMiDs. For example, thrombocytopenia, anemia, and neutropenia are common adverse events associated with proteasome inhibitors.[187, 207-209] Chemotherapy is also known to have myelosuppressive effects.[210, 211] The inclusion of all IMiDs in one group does, however, assist with counterfactual model sequential positivity, as patient groups contraindicated for lenalidomide (e.g., those refractory to lenalidomide) may still be prescribed pomalidomide.[123] Future analyses may consider more specifically-defined exposure and active comparator definitions (e.g., specific drugs, combinations, and doses) to address issues with consistency. This type of analysis may not be possible in the Flatiron database given sample size limitations.

Overall, this analysis informs whether relapsed MM patients who are sequentially exposed to IMiDs are at an increased risk of hematologic complications, compared with those who received IMiD-free regimens, which has important implications for real-world treatment decisions. Results suggest that sequential exposure to IMiDs across two LOTs may be mainly of concern for risk of severe cytopenias related to white blood cells, particularly neutrophils, and especially among those with recent histories. Although dose delays and infections due to cytopenia are unavailable for this cohort, results suggest that administering an IMiD-free regimen following an IMiD regimen may reduce severe cytopenia risk.

CHAPTER 4: INFLUENCE OF INCOMPLETE DEATH INFORMATION ON CUMULATIVE RISK ESTIMATES IN UNITED STATES CLAIMS DATA

Abstract

Background: Administrative claims databases often do not capture date or fact of death, so studies using these data may inappropriately treat death as a censoring event—equivalent to other withdrawal reasons—rather than a competing event. Understanding the influence of not distinguishing between disenrollment and death on cumulative risk estimates is necessary to inform evaluations of real-world data suitability.

Objective: To investigate the influence of specifying death as a censoring event versus competing event on cumulative risk estimates.

Method: We examined 1-, 3-, and 5-year cumulative risk of a composite outcome (myocardial infarction, stroke, and hospitalization for congestive heart failure) among initiators of antihypertensive medications telmisartan (exposure) and ramipril (referent) ages ≥55 in Optum claims, which reliably captures death, from 2003 to 2020. The cohort was created according to eligibility criteria of a published real-world data emulation of a randomized clinical trial (NCT00153101). Inverse probability of treatment weighting was used to adjust for patient characteristics. Censoring occurred upon disenrollment or end of study. We compared cumulative risk estimates from models where death was treated as a censoring event (cause-specific risk) versus competing event (sub-distribution risk). We examined whether the absolute difference between the two estimates depended on age strata and mortality rate in the claims-based analysis and in simulations.

Results: 34,527 patients were included (7,282 telmisartan, 27,245 ramipril). 5,495 events occurred over 86,629 person-years. Mortality rates per 1,000 person-years were 8.7 for ages 55–64, 22.2 for ages 65–74, and 68.9 for ages ≥75. The difference in cumulative risks increased over time, as event and mortality risks increased. Results were similar for both exposure

groups. For ramipril users (selected results), sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 16.9 (16.3, 17.4) and 17.4 (16.8, 18.0) at year 3 (difference = 0.6) and were 24.2 (23.5, 25.0) and 25.5 (24.7, 26.3) at year 5 (difference = 1.3). The increase in the difference in cumulative risks over time was greatest for the oldest age group: among ramipril users, 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 16.2 (15.1, 17.3) and 16.4 (15.3, 17.5) among ages 55–64 (difference = 0.2) and were 39.7 (37.9, 41.4) and 43.2 (41.3, 45.2) among ages ≥75 (difference = 3.6). Simulation results, from both fully synthetically simulated and plasmode-simulated cohorts, demonstrated the differences in cause-specific versus sub-distribution cumulative risks to increase with increasing mortality rate.

Conclusions: Differences in cumulative risks due to censoring of death, as compared to treating death as a competing event, increased with greater follow-up time and older age, where event and mortality risks were higher, in both claims-based and simulation-based approaches. We suggest researchers consider baseline cohort mortality risk associated with treatment indication when deciding whether real-world data with incomplete death information can be used without concern.

Background

Healthcare claims databases are a useful source of real-world data for pharmacoepidemiologic research, as unique identifiers allow patients to be tracked longitudinally while their varied providers continue to record diagnoses and prescribe medications. A main limitation of claims databases is the potential lack of a stable patient population due to the constant enrollment and disenrollment of members of the health plan (i.e., due to change/loss of employment, employer changing health plans), which is common among those who are commercially insured.[212] Patient outcomes can only be tracked in healthcare claims databases so long as an individual is enrolled in the health plan; loss to follow-up occurs upon health plan disenrollment. Difficulties arise when attempting to use claims data to examine the safety or effectiveness of a drug product that is expected to have a long induction period when confronted with loss to follow-up. Further complications arise because loss to follow-up occurs for heterogeneous reasons, which are typically unknown to the researcher. Insurance plan members exhibiting use of preventative healthcare services (e.g., influenza vaccination, screening tests) and those with chronic diseases and new cancer diagnoses have been observed to be more likely to remain enrolled in their health plan.[213-215] Experience of acute conditions (e.g., myocardial infarction, stroke, coagulopathy), emergency department visits, and overnight hospitalizations, however, have been associated with increased risk of within-year health plan disenrollment. This disenrollment could have been due to patient death, which was not well-captured.[215] Age, geographic region, and health insurance plan type, a proxy for socioeconomic status, are also related to disenrollment behavior.[215, 216]

Longitudinal analysis in claims data is further complicated by the fact that health plan disenrollment may not be readily distinguishable from patient death. The distinction between disenrollment and death has important implications for pharmacoepidemiologic research. When a patient disenrolls from their health plan, and either enrolls in an alternative health plan, or

remains alive and uninsured, the researcher is unable to observe the occurrence of the outcome of interest and the observation is therefore censored. Alternatively, if the patient dies before the outcome has occurred, the patient will never be able to experience the outcome and therefore has experienced a competing event (i.e., event that precludes the outcome of interest).

The Optum Research Database and the Truven MarketScan Research Database are two of the largest national, commercial administrative healthcare databases in the United States and both are commonly used for pharmacoepidemiologic research. In the Optum Research Database, which is linked with supplemental death information from the Social Security Administration, it is possible to identify individuals whose health plan enrollment ceases due to death, and therefore death may be appropriately specified as a competing event. Censoring occurs for patients whose disenrollment reason is not death (regardless of whether they subsequently die). In contrast, the Truven Health MarketScan Commercial Database does not capture complete death information, such that an individual who dies outside of the healthcare setting will appear the same as an individual who has disenrolled for other reasons. According to the Centers for Disease Control and Prevention, only 30% of all deaths occurred in an inpatient hospital facility in 2020.[217] The majority of deaths are therefore “ignored” as competing events and instead treated as censoring events because they appear the same as other causes of disenrollment.

When death is considered to be a censoring event, the usual Kaplan-Meier survival estimator quantifies a cause-specific risk of the outcome for a population in which a hypothetical intervention has eliminated death.[218] Individuals who experience the competing event are assumed to remain “biologically” at risk for the event of interest, but are removed from the risk set given that their unobserved follow-up removes them from being “methodologically” at risk for the outcome.[219] In this sense, individuals who die are treated in the same way as individuals who disenroll from their health plan and remain alive and biologically at risk of the outcome. The Kaplan-Meier estimator upweights future events by allocating each censored observation to all

subsequent events, implying that unobserved events occurred for censored individuals.[220] Alternatively, when the possibility that individuals may die without experiencing the outcome is taken into account, the sub-distribution risk can be estimated as the risk of the outcome in the presence of the naturally occurring competing event. Individuals who experience the competing event methodologically remain in the risk set, acting as a placeholder for the proportion of the population that cannot biologically experience the outcome.[218] In general, censoring patients who have experienced a competing event will yield a larger cumulative risk estimate than analyses accounting for the competing event via sub-distribution risks.[221-228] The magnitude of the difference between the cause-specific versus sub-distribution risks has been observed to be related to the competing event rate, the association between the exposure and the competing event, and the proportion of censoring due to the competing event.[224, 225, 229]

Despite established competing risk methodology, clinical studies often fail to address competing risks.[230-232] It is important to understand the influence of the inability to distinguish between disenrollment and death, as compared to the ability to specify death as a distinct competing event, on cumulative risk estimates. We explore whether the influence may depend on patient age strata and the underlying population mortality rate, as part of a claims-based analysis as well as a series of simulations in which more extreme mortality rates can be observed, to inform future analytic choices with these databases. Given knowledge of a patient cohort's underlying risk of death at various time points of interest, these results will advise whether we (a) need to use a data source with complete death information for event risk estimates or (b) can use a data source without complete death information available without worrying that the competing event of death will substantially influence event risk estimates. The ability to predict how results may change under various scenarios when death information is incomplete will be vital for generating informative real-world evidence and for ensuring the delivery of reliable treatment information to patients, providers, and healthcare practices.

Methods

We created a claims-based cohort to examine the influence of treating death as a censoring event, as compared to a competing event, on cumulative risk estimates both overall and according to patient age group. Given that not only mortality rate, but also outcome and censoring rates, may differ between age groups, we then conducted a series of simulations to determine whether the impact of not specifying death as a competing risk depends specifically on mortality rate. Finally, an exploratory analysis was performed in which the strength and directionality of the associations between a predictor variable with death and with disenrollment were varied to examine the interplay of the rates of these events. The details of these analyses are provided below.

Data Source

The claims-based analysis used the Optum Clinformatics® Data Mart (CDM), a proprietary research database containing de-identified medical and pharmacy claims of insured United States employees and their dependents from affiliated commercial and Medicare Advantage plans. There were approximately ten million annual patients in the database from April 2000 through December 2020, and a total of 83.7 million unique patients. Linkage of the Optum database to the Social Security Administration Death Master File, which captures death data from funeral directors, postal authorities, financial institutions, and relatives of deceased individuals, supplements death information from discharge statuses and diagnosis codes.

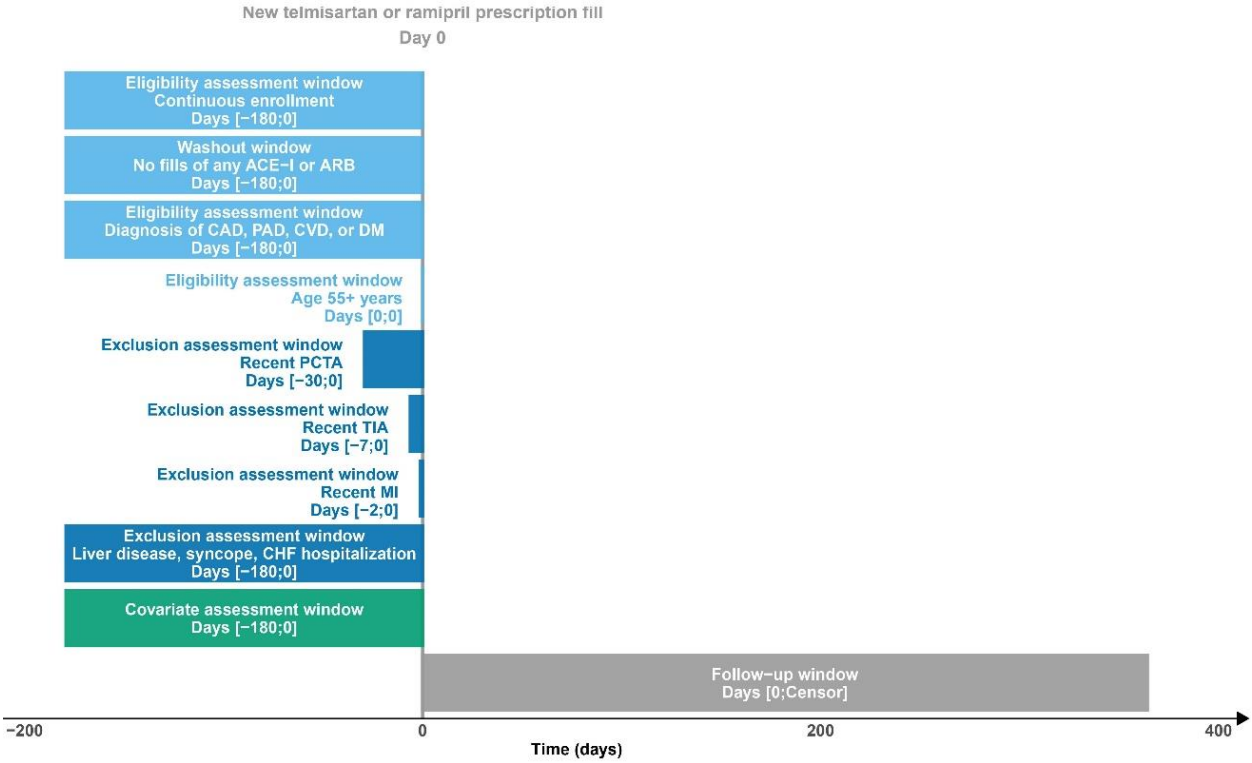
Study Population

An active comparator, new user cohort was created according to inclusion/exclusion criteria of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), using Optum data from 01 January 2003 through 31 March 2021 (the latest data availability at the time of study initiation). The ONTARGET trial was a randomized, active-

controlled, multinational, double-blind study testing the comparative efficacy of anti-hypertensive drugs telmisartan and ramipril for reducing the risk of cardiovascular adverse events (ClinicalTrials.gov: NCT00153101).[233, 234] Chronic hypertension is an established risk factor for cardiovascular morbidity and mortality.[235, 236] Various anti-hypertensive treatment options are available, including angiotensin-converting enzyme inhibitor (ACE-Is; e.g., ramipril) or angiotensin receptor blocker (ARBs; e.g., telmisartan), which address hypertension by lowering blood pressure. These varied hypertension treatment options may have different associations with the cardiovascular complications of hypertension. Prior to the ONTARGET trial, ACE-Is had been shown to reduce cardiovascular adverse events in patients with vascular disease, but the role of ARBs for this indication in this patient population was not known.[233] The primary objective of the ONTARGET trial was therefore to determine whether telmisartan was at least as effective as ramipril at reducing risk of cardiovascular events. The results of ONTARGET supported the receipt of a secondary approval for telmisartan for cardiovascular risk reduction.[237]

The ONTARGET trial population, which represents a population at a fairly high risk for vascular events, has previously been replicated in MarketScan by Fralick et al., notably limited by the inability to account for patient death as a competing event (however, the exclusion of individuals with a limited life expectancy from the study cohort likely limited the occurrence of this competing event).[238, 239] We chose this example as we were interested in applying this research question to a real-world example for which the lack of death information may have been important. The claims-based study replication by Fralick et al. was part of an effort to determine whether administrative healthcare data can achieve similar results as corresponding randomized clinical trials. The variable definitions of this high-profile study are well-described, and used the International Classification of Diseases, 9th Revision (ICD-9) only. Given our study period, conversion of the 10th Revision (ICD-10) was undertaken using forward and reverse mapping algorithms.[238] The schema for cohort creation is displayed in **Figure 28**.

Figure 28. Summary of inclusion criteria and baseline covariate assessment timing for Optum cohort of initiators of telmisartan or ramipril



ARB: angiotensin receptor blocker; ACE-I: angiotensin converting enzyme inhibitor; CAD: coronary artery disease; CHF: congestive heart failure; CVD: cerebrovascular disease; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral artery disease; PTCA: percutaneous transluminal coronary angiography; TIA: transient ischemic attack
Figure generated based on Schneeweiss et al. (2019).[240]

Patients 55 years or older who filled a new prescription of telmisartan or ramipril (both used for the treatment of hypertension) between 01 January 2003 and 31 March 2020 after 180 days (baseline period) of continuous enrollment in a participating health plan with no fills for any ACE-I or ARB were eligible for cohort inclusion. Cohort entry ended on 31 March 2020 to ensure a minimum of one year of potential follow-up until the end of data availability. The index date was defined as the date of the prescription fill. All patients were required to have a diagnosis of coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes mellitus during the baseline period, in accordance with ONTARGET. Consistent with the trial design, patients were excluded if they had a diagnosis of liver disease, syncope, stroke, or subarachnoid hemorrhage, or a hospitalization for congestive heart failure during the baseline period. Additionally, patients with recent myocardial infarction (within 2 days before the index

date), transient ischemic attack (within 7 days before the index date), or percutaneous transluminal coronary angioplasty (within 30 days before the index date) were also excluded. Although Fralick et al., consistent with the ONTARGET trial design, excluded individuals with a limited life expectancy (i.e., those with a cancer diagnosis, or living in a hospice, palliative care facility, or a nursing home), we relaxed this exclusion criteria and instead included this variable as a covariate so that we could ensure sufficient patient deaths were observed in the cohort. The codes used to define the cohort inclusion criteria are included in **Table 31**. All variables were defined according to the presence of one inpatient or two outpatient diagnosis codes (at least one day apart, with the maximum number of days apart specified according to the variable assessment period), in any position.

Table 31. Algorithms for study inclusion criteria and covariates

Characteristic	ICD-9 Diagnosis Codes	ICD-10 Diagnosis Codes	Other
Acute myocardial infarction	410	I21	NA
Angina	411, 413	I20, I24, I25.110, I25.700, I25.710, I25.720, I25.730, I25.790	NA
Anxiety	293.84, 300.0, 300.2, 300.3, 308.0, 309.24, 309.81	F06.4, F40–F42, F43.0, F43.10, F43.12, F43.22	NA
Asthma	493	J45	NA
Atrial fibrillation	427.31	I48.91	NA
Coronary artery bypass graft or percutaneous coronary intervention	V45.81, V45.82 *Procedure codes:* 00.66, 36	Z95.1, Z98.61 *Procedure codes:* O210–O213, O21K0Z, 21L, O270–O273, 02C0–02C3, 02QB3ZZ, 02QB4ZZ, 02QC3ZZ, 02QC4ZZ, 3E07017, 3E070PZ, 3E07317, 3E073PZ	*CPT:* 33510–33523, 33533–33536, 92982 92995, 92980, 92981 *HCPCS*: G0290, G0291
Cancer	140–165, 170–175, 179–203, 238.6, 273.3	C00–C26, C30–C34, C37–C41, C43–C45, C47–C58, C60–C86, C88, C90, C91, C96, D47.Z9	NA
Cerebrovascular disease	362.34, 430–438	G45–G46, H34.0, I60–I69	NA
Chronic obstructive pulmonary disease	491, 492, 496	J41–J44	NA
Colonoscopy	*Procedure codes:* 45.23	*Procedure codes*: 0DJD8ZZ	*CPT:* 45378–45392 *HCPCS:* G0105
Congestive heart failure	398.91, 402.x1, 403.x1, 403.x3, 428	I09.81, I11.0, I13.0, I13.2, I50	NA
Coronary artery disease	413, 414.0 *Procedure codes:* 36.0, 36.19, 36.2	I20.1, I20.8, I20.9, I25.10, I25.70–I25.81 *Procedure codes:* 0210–0213, 0270–0273, 02C0–02C3, 3E07	*CPT*: 33510–33536, 92986, 92987
Creatinine test	NA	NA	*CPT:* 82565
Dementia	290, 294, 330, 331	E75.0–E75.1, E75.25, E75.29, E75.4, F01.5, F02.80, F02.81, F03.90, F03.91, F04, F06.1, F06.8, F84.2, G30, G31, G91, G93.7, G94	NA
Depression	293.83, 296.2–296.3, 298.0, 300.4, 309.0, 309.1, 309.28, 311	F06.30, F32 (not F32.8), F33 (not F33.9), F34.1, F43.21, F43.23	NA
Diabetes mellitus	250	E11, E13	NA
Fecal occult blood test	NA	NA	*CPT*: 82270, 82274

Characteristic	ICD-9 Diagnosis Codes	ICD-10 Diagnosis Codes	Other
			HCPCS: G0107, G0328
Hemoglobin A1C test	NA	NA	*CPT:* 83036
Hemorrhagic stroke	430, 431	I60, I61	NA
Hyperlipidemia	272.0, 272.2, 272.4	E78.0, E78.2, E78.4, E78.5	NA
Hypertension	401, 403	I10, I12, I16.9	NA
Influenza vaccine	V04.8, V04.81, V06.6	Z25.1	*CPT:* 90655, 90656, 90657, 90658, 90660 *HCPCS:* G0008
Ischemic heart disease	410, 411.0, 412, 414, 429.71, 429.79	I21–I22, I23.0, I24.0, I24.1, I25.9, I51.0	NA
Ischemic stroke	433.x1, 434.x1	I63	NA
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570–572, 573.3, 573.4, 573.8, 573.9, V42.7	B18, I85, I86.4, K70, K71.1, K71.3, K71.4, K71.5, K71.7, K72–K74, K76.2–K76.9 (not K76.82), Z94.4	NA
Metabolic panel	NA	NA	*CPT:* 80053
Obesity	278.00, 278.01, 278.03, 539, 649.1, 649.2, V85.3, V85.4	E66, K95, O99.21, O99.84, Z68.3–Z68.4	*CPT:* 43644, 43645, 43770, 43842, 43843, 43845, 43846, 43847, 43999 *Drugs:* benzphetamine hydrochloride, diethylpropion hydrochloride, orlistat, phendimetrazine tartrate, phentermine hydrochloride, sibutramine hydrochloride monohydrate
Osteoarthritis	715	M15–M19	NA
Other renal disease	274.10, 403, 404, 440.1, 442.1, 453.3, 572.4, 580, 587, 593, 753.0, 753.3, 791.2, 791.3, 866.00, 866.01, 866.1	I12, I13, I70.1, I72.2, I82.3, K76.7, M10.30, N00, N01, N13, N13 (not N13.2, N13.3, N13.6), N26.9, N28 (not N28.84–N28.86), Q60.5, Q60.6, Q63, R82.1, R82.3, S37.001A, S37.002A, S37.009A, S37.011A, S37.012A, S37.019A, S37.021A, S37.022A, S37.029A	NA
Peripheral vascular disease	785.4, 093.0, 437.3, 440, 441, 443, 444.2, 444.81, 447.1, 557.1, 557.9, V43.4 *Procedure codes:* 38.48	I70, I71, I73.1–I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	*CPT*: 37205, 75962
Pneumonia	480–486, 487.0, 507	A22.1, A37.x1, B25.0, B44.0, B77.81, J10.0, J11.0, J12–J18, J69	NA
Prostate antigen test	NA	NA	*CPT:* 4152, 84153, 84154 *HCPCS:* G0103
Sepsis	038, 995.91, 995.92	A40.3, A40.9, A41, R65.20, R65.21	NA
Sleep apnea	327.23	G47.33	NA
Sleep disorder	307.4, 327.0, 327.2, 347, 780.5	F51, G47.0, G47.10, G47.20, G47.3–G47.4, G47.8, G47.9	NA
Smoking	305.1, 649.0, 989.84, V15.82	F17.200, O99.33, T65.2xxA, Z87.891	*CPT:* 99406, 99407 *HCPCS:* S9075, S9453 *Drugs:* nicotine, varenicline tartrate
Syncope	780.2	R55	NA
Thyroid function test	NA	NA	*CPT:* 84436, 84439, 84443, 84479, 80091, 80092
Transient ischemic attack	435	G45, G46.0, G46.1, G46.2, I67.84	NA
Transthoracic echocardiogram	*Procedure codes:* 88.72, 00.24	*Procedure codes:* B240ZZ3, B241ZZ3, B244, B245, B246, B24D	*CPT:* 93306–93308, 93312–93318, 93320, 93321, 93350, 93351, 93355, 93662
Urinary incontinence	788.3, 788.91	N39.3–N39.4, R32, R39.81	NA

CPT: Current Procedural Terminology. HCPCS: Healthcare Common Procedure Coding System. ICD-9: International Classification of Diseases, Ninth Revision. ICD-10: International Classification of Diseases, Tenth Revision. NA: Not applicable.

Outcome

The outcome of interest was defined as a composite outcome of the following cardiovascular safety events, according to the primary discharge diagnosis code for an inpatient visit: myocardial infarction, stroke, and hospitalization for congestive heart failure (**Table 32**). This definition is consistent with the ONTARGET trial primary endpoint.

Table 32. Composite cardiovascular safety outcome algorithm

Composite Outcome Component	ICD-9 Diagnosis Codes	ICD-10 Diagnosis Codes
Myocardial infarction	410.xx	I21
Stroke	430, 431, 433.x1, 434.x1, 436	I60, I63, I67.89
Hospitalization for congestive heart failure	398.91, 402.x1, 404.x1, 404.x3, 428.x	I09.81, I11.0, I13.0, I13.2, I50

ICD-9: International Classification of Diseases, Ninth Revision. ICD-10: International Classification of Diseases, Tenth Revision.

Exposure

The study medication of interest was the ARB telmisartan (Micardis), which was approved as an antihypertensive medication in 1998. Telmisartan may be prescribed alone or in combination with other antihypertensive agents, and is typically administered as a once daily oral dose of 40 milligrams.[241] The comparator medication was the ACE-I ramipril (Altace), which was approved to treat hypertension in 1991. Ramipril is normally administered as a 10 milligram once daily oral dose, although patients are usually initiated at lower dosages to ensure it is well-tolerated.[242] Both medications have similar toxicity and adverse event profiles. For this analysis, patients who initiated telmisartan either as monotherapy or in combination with other antihypertensive medications (except for ramipril) were both considered to meet cohort entry criteria.

Exposure was treated as time-fixed, according to assignment at index (initial prescription fill date); telmisartan versus ramipril status was assumed to remain constant throughout the follow-up period, such that treatment discontinuation and exposure group switches and were not considered. Although this differs from the exposure definition used in the Fralick et al. cohort

(which defined treatment according to assignment at index, with added censoring variables for treatment switching and discontinuation during the follow-up period), we decided to define exposure based on treatment initiation alone for simplicity given that estimation of the treatment effect was not the primary goal of this study. We did not incorporate additional censoring variables for treatment switching and discontinuation, so that the analyses could focus on the relationships between the study outcome, death, disenrollment, and their respective predictors.

Covariates

To address confounding, we adjusted for about 70 patient characteristics (**Table 33**), as specified by Fralick et al., by using inverse probability of treatment weighting.[238] Although this differed from the propensity score matching method used by Fralick et al., inverse probability of treatment weighting allowed for preservation of the sample size, which was important for ensuring we were able to evaluate the influence of mortality in this cohort. The demographic characteristics, measures of healthcare utilization, concomitant medication use, and comorbidities specified in **Table 33** were measured during the six months before the index date (baseline period) and included in the inverse probability of treatment weighting model. The codes used to define the baseline comorbidities are included in **Table 31** and the drugs used to define baseline medication use are included in **Table 34**. All baseline comorbidities were defined according to the presence of one inpatient or two outpatient diagnosis codes (minimum one day apart, maximum 180 days apart), in any position.

Table 33. List of baseline characteristics

Category	Characteristics	
Demographic characteristics	• Age • Sex	• Year of cohort entry
Healthcare utilization	• Any general practitioner visits • Any emergency department visits • Any cardiologist visits • Number of unique medications dispensed • Prostate specific antigen test • Colonoscopy	• Fecal occult blood test • Influenza vaccine • Hemoglobin A1C test • Creatinine test • Comprehensive metabolic panels • Thyroid function test • Transthoracic echocardiograms
Baseline medication use	• Angiotensin converting enzyme inhibitors • Angiotensin receptor blockers • Antiarrhythmics • Anticonvulsants • Antidepressants • Antihyperlipidemic medications • Antiparkinsonian medications • Antiplatelet agents • Antipsychotics • Anxiolytics/hypnotics • Benzodiazepines • Beta-blockers • Bisphosphonates • Calcium channel blockers	• Chronic obstructive pulmonary disease/asthma medications • Cox-2 inhibitors • Digoxin • Heparins • Loop diuretics • Nitrates • Nonsteroidal anti-inflammatory drugs • Opioids • Oral anticoagulant • Oral steroids • Other diuretics • Statins • Thiazides
Baseline comorbidities	• Acute myocardial infarction • Angina • Anxiety • Asthma • Atrial fibrillation • Congestive heart failure • Chronic obstructive pulmonary disease • Coronary artery bypass graft/percutaneous coronary intervention • Dementia • Depression • Diabetes • Hemorrhagic stroke • Hyperlipidemia • Hypertension	• Ischemic heart disease • Ischemic stroke • Limited life expectancy (those with a cancer diagnosis, or living in a hospice, palliative care facility, or a nursing home) • Obesity • Obstructive sleep apnea • Osteoarthritis • Peripheral vascular disease • Pneumonia • Renal disease (non-diabetic) • Sepsis/septicemia • Sleep disorder • Smoking • Transient ischemic attack • Urinary incontinence

Table 34. Baseline medication use definitions

Medication Class	Drugs
Angiotensin converting enzyme inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin receptor blockers	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Antiarrhythmics	Amiodarone, dofetilide, dronedarone, flecainide, ibutilide, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide
Anticonvulsants	Carbamazepine, divalproex, eslicarbazepine, ethotoin, ethosuximide, ezogabine, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, methsuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide
Antidepressants	Amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, fluoxetine, fluvoxamine, imipramine, isocarboxazid, levomilnacipran, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypropine, trazodone, trimipramine, venlafaxine, vilazodone, vortioxetine
Antihyperlipidemic	Alirocumab, cholestyramine, clofibrate, colesevelam, colestipol, ethyl eicosapentaenoic acid, ezetimibe, evolocumab¸ fenofibrate, gemfibrozil, haloperidol, lomitapide, mipomersen, niacin, nicotinamide, omega-3 acid ethyl esters
Antiparkisons	Amantadine, benztropine, biperiden, carbidopa, levodopa, pergolide, pramixepole, procyclidine, rasagiline, ropinirole, rotigotine, tolcapone, trihexyphenidyl
Antiplatelets	Aspirin, clopidogrel, cilostazol, dipyridamole, prasugrel, ticlopidine, ticagrelor
Antipsychotics	Aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, mesoridazine, molindone, olanzapine, paliperidone, perphenazine, pimozide, promazine, propiomazine, quetiapine, risperidone, thioridazine, thiothixene, trifluprom azine, trifluoperazine, ziprasidone
Anxiolytics	Buspirone, chloral hydrate, diphenhydramine, doxylamine, eszopiclone, ethclorvynol, glutethimide, meprobamate, methaqualone, zaleplon, zolpidem
Benzodiazepines	Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam
Beta-blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, propranolol, penbutolol, pindolol, sotalol, timolol
Bisphosphonates	Alendronate sodium, alendronate sodium/cholecalciferol (vitamin d3), etidronate disodium, ibandronate sodium, pamidronate disodium, risedronate sodium, risedronate sodium/calcium carbonate, zoledronic acid
Calcium channel blockers	Amlodipine, bepridil, clevidipine, diltiazem, felodipine, isradipine, mibefradil, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil
COPD Ashma Med	Albuterol, arformoterol, budesonide/formoterol, formoterol, fluticasone/salmeterol, ipratropium, levalbuterol, metaproterenol, mometasone/formoterol, montelukast, pirbuterol,salmeterol, terbutaline, theophylline, tiotropium, zafirlukast, zileuton
Cox-2 inhibitors	Celecoxib, rofecoxib, valdecoxib
Digoxin	Digoxin
Heparins	Heparin, dalteparin, enoxaparin, tinzaparin
Loop diuretics	Bumetanide, ethacrynic acid, furosemide, torsemide
Nitrates	Isosorbide dinitrate, isosorbide mononitrate, nitroglycerin
NSAIDs	Diclofenac, etodolac, flurbiprofen, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen, piroxicam, sulindac
Opioids	Codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone, propoxyphene, tramadol
Oral anticoagulants	Apixaban, dabigatran, rivaroxaban, warfarin
Oral steroids	Betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, triamcinolone
Other diuretics	Amiloride, eplerenone, spironolactone, triamterene
Statins	Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, lovastatin niacin, ezetimibe simvastatin, pravastatin aspirin, pitavastatin
Thiazides	Bendroflumethiazide Chlorothiazide Chlorthalidone Hydrochlorothiazide Hydroflumethiazide Indapamide Methyclothiazide Metolazone Polythiazide Trichlormethiazide

Statistical Analyses

The analyses were conducted as follows: (1) we compared estimates of the absolute treatment effect on a composite cardiovascular outcome when death was a censoring event versus competing event in the Optum cohort, (2) we evaluated whether the difference in treatment effect estimates depended on age stratum in the Optum cohort, (3) we evaluated whether the treatment effect estimate differences depended on the underlying mortality rate of the population in fully-simulated cohorts, (4) we evaluated whether the differences in treatment effect estimates depended on the underlying mortality rate of the population in plasmode-simulated cohorts, and (5) we evaluated whether the differences in treatment effect estimates depended on predictors of death and disenrollment in fully-simulated cohorts.

First, using the Optum cohort, we emulated the treatment effect as generated in Fralick et al.[238] We examined the cumulative risks and risk differences (at 1, 3, and 5 years) of the composite study outcome among initiators of telmisartan versus ramipril. Patients were followed up from the date of their prescription fill (index date) until the earliest occurrence of the outcome of interest, disenrollment from the health plan, death, or the administrative end of the study period. Censoring occurred upon disenrollment from the health plan or the end of the study period. We assumed these occurrences of loss to follow-up to be differential, given that disenrollment, exposure assignment, and incidence of the outcome are expected to be common effects of various measured and unmeasured characteristics (e.g., demographic characteristics, chronic diseases, acute conditions).[213-216, 243] Given the assumed informative censoring, we included an inverse probability of censoring weighting model, which included the same list of covariates included in the inverse probability of treatment weighting model.[243]

We varied whether death was treated as a competing event or a censoring event. Cumulative outcome risks were estimated in two ways:

1. Cause-specific cumulative risk functions were estimated according to the Kaplan Meier estimator.[244] Death was specified as a censoring event, in addition to disenrollment before death. Death times were folded under disenrollment such that if death occurred before disenrollment, death time was assigned as disenrollment time, as it would appear in a database without death information. The cause-specific cumulative risk function was estimated as the complement of the Kaplan Meier survival estimator, which is given by:[245]

$$S(t) = \prod_{t_k<t} \left(1 - \frac{d(t_k)}{n(t_k)}\right)$$

Where $d(t_k)$ is the number of events at time t_k and $n(t_k)$ is the number at risk at time t_k.

2. Sub-distribution cumulative risk functions were estimated according to the Aalen-Johansen estimator.[184] Death was specified as a competing event and disenrollment before death was specified as a censoring event. The Aalen-Johansen cumulative risk function is given by:[245]

$$R_j(t) = \sum_{t_k<t} S(t_k - 1)\frac{d_j(t_k)}{n(t_k)})$$

Where $S(t)$ is the Kaplan-Meier survival function at time t, $d_j(t_k)$ is the number of events of type $J = j$ at time t_k, and $n(t_k)$ is the number at risk at time t_k.

At each increment of follow-up (1, 3, and 5 years), we calculated the difference between the cause-specific estimator and the sub-distribution estimator for both treatment-specific cumulative risks and for the risk differences (telmisartan versus ramipril, consistent with the ONTARGET trial design). Confidence intervals for the difference in cumulative risks and the difference in risk differences were calculated based on 2,000 bootstrap resamples from the Optum cohort. It is worth noting that we assumed all death events to be completely captured

and specified as competing events. In actuality, it is possible that death events may have been undercounted, in which case missed death events would have been inadvertently treated as censoring events. We discuss this in more detail as part of the study limitations.

Next, we performed an age-stratified analysis, repeating the above analyses for three age groups: (1) 55 to 64 years, (2) 65 to 74 years, and (3) 75 years or greater. The differences between treatment effect estimates when specifying death as a competing event versus as a censoring event were expected to be greater in older age strata, where the mortality and outcome rates were higher, compared with younger age strata.[246, 247] All analyses were completed using the "causalRisk" R package.[248]

Simple Simulation

Given that older age strata may be associated with higher outcome rates in addition to higher mortality rates, we next conducted a series of simulations to determine the influence of mortality rate specifically on the difference between cause-specific and sub-distribution risk estimates.[246, 247] We explored various alternative mortality rates that may be consistent with other patient cohorts. We created fully synthetic simulated cohorts according to parameters observed in the Optum cohort. Simulations were completed using the R package "lava," which uses structural equation models with latent variables.[249] A binary exposure corresponding to telmisartan (X = 1) or ramipril (X = 0) was generated from a binomial distribution with P(X = 1) = 0.20. Times to composite cardiovascular safety endpoint (Y_1: scale = 0.00021, shape = 0.90), death (Y_2: scale = 0.0000024, shape = 1.23) or disenrollment (Y_0: scale = 0.00071, shape = 1.02) were simulated according to Cox Weibull distributions. Dummy variables were created for a single categorical confounder, which was generated according to the observed age distribution in the Optum cohort (C_1: ages 65–74 years [35%]; C_2: ages 75+ years [23%]; ages 55–64 years as reference group). The associations between treatment and the predictor variables (treatment and age) were simulated according to logistic regression models, using the observed odds

ratios (ORs) from the Optum cohort with the youngest age group as the reference group (OR = 1.34 for 75+ years; OR = 1.43 for 65–74 years). The associations between death and the predictor variables (treatment and age) were simulated according to a proportion hazards regression model, using the observed hazard ratios (HRs) from the Optum cohort (HR = 0.87 for treatment; HR = 2.83 for 65–74 years; HR = 8.80 for 75+ years). The associations between disenrollment and the predictor variables (treatment and age) were simulated according to a proportional hazards regression model, using the observed hazard ratios from the Optum cohort (HR = 1.15 for treatment; HR = 0.64 for 65–74 years; HR = 0.50 for 75+ years). Finally, the associations between the composite cardiovascular safety event and the predictor variables (treatment and age) were simulated according to a proportional hazards regression model, using the observed hazard ratios from the Optum cohort (HR = 0.93 for treatment; HR = 1.64 for 65–74 years; HR = 3.16 for 75+ years). Death rates were manipulated by multiplying the scale parameter of the Cox Weibull distribution for time to death to double and triple the mortality rate. We examined the impact of doubling and tripling the mortality rate on the cumulative risk of the cardiovascular safety endpoint according to the cause-specific and sub-distribution models. The models were constructed as previously described and incorporated inverse probability of treatment and censoring weighting models, both of which included only age category. For each scenario, we generated 1,000 Monte Carlo simulations and calculated the difference between the cause-specific estimator and the sub-distribution estimator at each time, averaged across all simulations.

Plasmode Simulation

We then conducted plasmode simulations as an expansion of the simulation work described above.[250] Many important features of healthcare claims are not completely understood, and therefore cannot be replicated in fully synthetic simulated data (e.g., numerous covariates with complex covariance structures, intricate patient follow-up and censoring patterns). To address

this complexity, plasmode simulations start with real data sets, generated from natural processes, and augments them with simulated data. The plasmode simulation approach is advantageous as it allows the investigator to manipulate features such as event rates, confounding strength, and exposure effect, while maintaining a realistic data set with resemblance to the observed complex data structure.[250-252]

We sampled individuals with replacement from the Optum cohort and maintained the existing covariate values. The observed covariate structure was used to predict time to death, under the baseline, double, and triple mortality rates. We examined the impact on the cumulative risk of the cardiovascular safety endpoint according to the cause-specific and sub-distribution models under each mortality rate manipulation. The models were constructed as previously described and incorporated inverse probability of treatment and censoring weighting models, both of which included the full list of confounder variables from the primary analysis (**Table 33**). For each scenario, we generated 1,000 Monte Carlo simulations of 34,000 individuals (approximate estimated sample size of Optum cohort). The average difference between each estimator was calculated at each time as the difference between the cause-specific estimator and the sub-distribution estimator, averaged across all simulations.

Exploratory Analysis

As an exploratory analysis, we investigated the impact on the resulting difference between the cause-specific and sub-distribution cumulative risks of a predictor variable's relationship with death and disenrollment as part of a fully synthetic simulation. Manipulating the strength and directionality of the associations between a predictor variable with death and with disenrollment allowed for examination of the interplay of the rates of these events, as compared to previous simulation analyses in which the mortality rate was manipulated in isolation. There is a wide variety of patient characteristics available in healthcare claims databases, which may be strong predictors of death and/or disenrollment. This exploratory analysis was targeted at exploring the

situation in which a given data source is missing information on death, but information is available on characteristics that are strongly related to death. Hypothesizing about potential variables that are strongly related to death, and, further, whether these variables are also strongly related to disenrollment, may help contribute to research decisions regarding whether a data source with incomplete death information is fit for regulatory purpose.

The base cohort was created according to the parameters of the simple simulation described above. We additionally introduced a binary variable X with P(X = 1) = 0.50, which was associated with neither the exposure nor the outcome and therefore was not included in subsequent inverse probability weighting models. In the baseline model, X was set to be associated with neither death nor disenrollment (HR = 1.0 for death; HR = 1.0 for disenrollment). We then manipulated the magnitude and directionality of the associations between X with death and with disenrollment in three key ways: (1) strong protective association with both [HR = 0.2 for death; HR = 0.2 for disenrollment], (2) strong harmful association with both [HR = 5.0 for death; HR = 5.0 for disenrollment], (3) strong associations with opposite directionality [HR = 5.0 for death; HR = 0.2 for disenrollment]. As an example, scenario (1) may be met by measures of preventative service utilization (although, likely not to the extent of the exemplar hazard ratios used here) such that a patient who is using preventative care services is likely to remain on their insurance (i.e., be less likely to disenroll) and also to be healthier (i.e., less likely to die). Scenario (2) may be met by an indicator of recent death of a patient's spouse (although unavailable in claims data, this type of measure could be present in other healthcare databases), which could be expected to strongly predict subsequent death of the patient as well as disenrollment from their health plan (i.e., if they were a dependent on their spouse's insurance plan). Finally, for scenario (3), a patient who is very sick and/or elderly is at an increased risk of death, but is unlikely to switch insurance given nearness to end of life. We examined the impact of each of these scenarios on the resulting cumulative risks of the

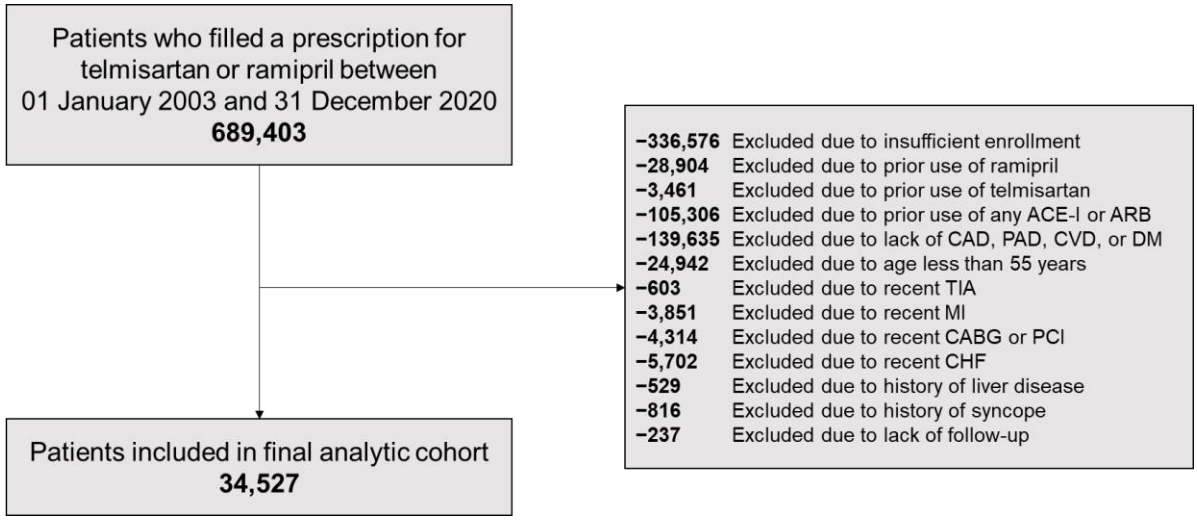
cardiovascular safety endpoint according to the cause-specific and sub-distribution models.

Results

Optum Cohort

There were 689,403 patients identified who filled a prescription for either telmisartan or ramipril between 01 January 2003 and 31 December 2020. Following the application of study inclusion and exclusion criteria, 34,527 patients remained and were included in the analytic cohort (7,282 telmisartan, 27,245 ramipril; **Figure 29**).

Figure 29. Summary of cohort enrollment of initiators of telmisartan or ramipril between 01 January 2003 and 31 December 2020 in Optum according to inclusion criteria



ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: congestive heart failure; CVD: cerebrovascular disease; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral artery disease; PCI, percutaneous coronary intervention; TIA: transient ischemic attack

Cohort characteristics before and after inverse probability of treatment weighting are displayed in **Table 35**. Compared to those prescribed telmisartan, patients prescribed ramipril were more likely to be male (ramipril 60%, telmisartan 44%), to enter the cohort between 2003–2008 (ramipril 52%, telmisartan 37%), and to have a history of CAGB or PCI (ramipril 6%, telmisartan 3%). Alternatively, telmisartan users were more likely than ramipril users to have hypertension (ramipril 50%, telmisartan 71%) and renal disease (ramipril 4%, telmisartan 7%) and to have

visited a general practitioner during the baseline period (ramipril 12%, telmisartan 18%). These characteristics were well-balanced after inverse probability of treatment weighting.

Table 35. Characteristics of Optum cohort of initiators of telmisartan or ramipril between 01 January 2003 and 31 December 2020 before and after inverse probability of treatment weighting

	Unweighted			Weighted		
Characteristic	**Ramipril n = 27,245**	**Telmisartan n = 7,282**	**SMD**	**Ramipril n = 34547.55**	**Telmisartan n = 34282.01**	**SMD**
Demographics						
Age, mean (SD)	67.2 (8.5)	68.5 (8.5)	-0.15	67.5 (8.6)	67.7 (8.4)	-0.02
Male	16,414 (60.3)	3,176 (43.6)	0.34	19,581 (56.7)	19,201 (56.0)	0.02
Cohort year						
2003–2008	14,171 (52.0)	2,697 (37.0)	0.38	16,866 (48.8)	16,566 (48.3)	0.01
2009–2014	7,987 (29.3)	2,099 (28.8)	0.00	10,101 (29.2)	10,071 (29.4)	0.00
2015–2020	5,087 (18.7)	2,486 (34.1)	0.00	7,581 (21.9)	7,636 (22.3)	0.00
Comorbidities						
Acute myocardial infarction	672 (2.5)	57 (0.8)	0.13	728 (2.1)	663 (1.9)	0.01
Angina	1,383 (5.1)	184 (2.5)	0.13	1,566 (4.5)	1,520 (4.4)	0.00
Anxiety	693 (2.5)	222 (3.1)	0.03	921 (2.7)	930 (2.7)	0.00
Asthma	661 (2.4)	252 (3.5)	0.06	914 (2.6)	966 (2.8)	0.01
Atrial fibrillation	1,616 (5.9)	279 (3.8)	0.10	1,906 (5.5)	2,159 (6.3)	0.03
COPD	1,651 (6.1)	452 (6.2)	0.01	2,117 (6.1)	2,174 (6.3)	0.01
CABG/PCI	1,698 (6.2)	211 (2.9)	0.16	1,907 (5.5)	1,853 (5.4)	0.00
Dementia	678 (2.5)	157 (2.2)	0.02	840 (2.4)	861 (2.5)	0.01
Depression	1,238 (4.5)	337 (4.6)	0.00	1,577 (4.6)	1,619 (4.7)	0.01
Diabetes mellitus	16,192 (59.4)	4,838 (66.4)	0.15	21,042 (60.9)	20,795 (60.7)	0.00
Hemorrhagic stroke	130 (0.5)	22 (0.3)	0.03	153 (0.4)	193 (0.6)	0.02
Hyperlipidemia	13,003 (47.7)	3,437 (47.2)	0.01	16,438 (47.6)	16,185 (47.2)	0.01
Hypertension	13,510 (49.6)	5,154 (70.8)	0.44	18,704 (54.1)	18,768 (54.8)	0.01
Ischemic heart disease	9,441 (34.7)	1,722 (23.7)	0.24	11,160 (32.3)	10,982 (32.0)	0.01
Ischemic stroke	858 (3.2)	192 (2.6)	0.03	1,057 (3.1)	1,139 (3.3)	0.02
Limited life expectancy	1,997 (7.3)	491 (6.7)	0.02	2,501 (7.2)	2,504 (7.3)	0.00
Obesity	1,157 (4.3)	510 (7.0)	0.12	1,670 (4.8)	1,700 (5.0)	0.01
Obstructive sleep apnea	632 (2.3)	331 (4.6)	0.12	962 (2.8)	976 (2.9)	0.00
Osteoarthritis	1,806 (6.6)	665 (9.1)	0.09	2,462 (7.1)	2,458 (7.2)	0.00
Peripheral vascular disease	2,671 (9.8)	794 (10.9)	0.04	3,470 (10.0)	3,524 (10.3)	0.01
Pneumonia	500 (1.8)	125 (1.7)	0.01	628 (1.8)	653 (1.9)	0.01
Renal disease (non-diabetic)	1,068 (3.9)	523 (7.2)	0.14	1,607 (4.7)	1,678 (4.9)	0.01
Sepsis/septicemia	232 (0.9)	72 (1.0)	0.01	311 (0.9)	314 (0.9)	0.00
Sleep disorder	1,333 (4.9)	519 (7.1)	0.09	1,858 (5.4)	1,886 (5.5)	0.01
Smoking	1,394 (5.1)	313 (4.3)	0.04	1,705 (4.9)	1,627 (4.8)	0.01
Transient ischemic attack	582 (2.1)	146 (2.0)	0.01	733 (2.1)	754 (2.2)	0.01
Urinary incontinence	229 (0.8)	76 (1.0)	0.02	306 (0.9)	307 (0.9)	0.00
Baseline medication use						
Antiarrhythmics	516 (1.9)	114 (1.6)	0.03	632 (1.8)	739 (2.2)	0.02
Anticonvulsants	2,381 (8.7)	769 (10.6)	0.06	3,142 (9.1)	3,008 (8.8)	0.01
Antidepressants	4,721 (17.3)	1,256 (17.3)	0.00	5,992 (17.3)	6,078 (17.7)	0.01
Antihyperlipidemic	3,831 (14.1)	1,002 (13.8)	0.01	4,852 (14.0)	4,971 (14.5)	0.01
Antiparkison	447 (1.6)	125 (1.7)	0.01	578 (1.7)	615 (1.8)	0.01
Antiplatelets	4,148 (15.2)	863 (11.9)	0.10	5,031 (14.6)	5,163 (15.1)	0.01
Antipsychotics	464 (1.7)	101 (1.4)	0.03	569 (1.7)	581 (1.7)	0.00
Anxiolytics	1,595 (5.9)	474 (6.5)	0.03	2,069 (6.0)	2,015 (5.9)	0.00
Benzodiazepines	2,603 (9.6)	729 (10.0)	0.02	3,346 (9.7)	3,356 (9.8)	0.00
Beta-blockers	10,082 (37.0)	2,750 (37.8)	0.02	12,847 (37.2)	12,968 (37.8)	0.01
Bisphosphonates	926 (3.4)	290 (4.0)	0.03	1,219 (3.5)	1,200 (3.5)	0.00

Characteristic	Unweighted			Weighted		
	Ramipril n = 27,245	Telmisartan n = 7,282	SMD	Ramipril n = 34547.55	Telmisartan n = 34282.01	SMD
Calcium channel blockers	4,292 (15.8)	2,040 (28.0)	0.30	6,352 (18.4)	6,432 (18.8)	0.01
COPD/asthma medication	2,368 (8.7)	766 (10.5)	0.06	3,150 (9.1)	3,309 (9.7)	0.02
Cox-2 inhibitors	1,043 (3.8)	192 (2.6)	0.07	1,236 (3.6)	1,256 (3.7)	0.00
Digoxin	407 (1.5)	91 (1.3)	0.02	500 (1.5)	484 (1.4)	0.00
Heparins	170 (0.6)	41 (0.6)	0.01	211 (0.6)	223 (0.7)	0.01
Loop diuretics	2,642 (9.7)	815 (11.2)	0.05	3,476 (10.1)	3,449 (10.1)	0.00
Nitrates	1,975 (7.3)	395 (5.4)	0.07	2,365 (6.9)	2,420 (7.1)	0.01
NSAIDs	3,147 (11.6)	1,022 (14.0)	0.07	4,172 (12.1)	4,146 (12.1)	0.00
Opioids	6,784 (24.9)	1,879 (25.8)	0.02	8,678 (25.1)	8,605 (25.1)	0.00
Oral anticoagulant	1,686 (6.2)	408 (5.6)	0.02	2,105 (6.1)	2,393 (7.0)	0.04
Oral steroids	3,113 (11.4)	1,017 (14.0)	0.08	4,150 (12.0)	4,123 (12.0)	0.00
Other diuretics	1,329 (4.9)	441 (6.1)	0.05	1,769 (5.1)	1,793 (5.2)	0.01
Statins	13,689 (50.2)	3,448 (47.4)	0.06	17,149 (49.6)	16,917 (49.4)	0.01
Thiazides	2,294 (8.4)	881 (12.1)	0.12	3,189 (9.2)	3,342 (9.8)	0.02
Healthcare Utilization						
General practitioner visit	3,197 (11.7)	1,322 (18.2)	0.18	4,519 (13.1)	4,437 (13.0)	0.00
Emergency department visit	5,194 (19.1)	1,369 (18.8)	0.01	6,571 (19.0)	6,681 (19.5)	0.01
Unique medications, mean (SD)	2.8 (-2.2)	3.0 (-2.2)	-0.09	2.9 (2.2)	2.9 (2.2)	-0.02
Cardiologist visits	1,648 (6.1)	536 (7.4)	0.05	2,182 (6.3)	2,200 (6.4)	0.00
Prostate specific antigen test	5,557 (20.4)	1,114 (15.3)	0.13	6,670 (19.3)	6,520 (19.0)	0.01
Colonoscopy	1,527 (5.6)	401 (5.5)	0.00	1,933 (5.6)	2,019 (5.9)	0.01
Fecal occult blood test	1,915 (7.0)	477 (6.6)	0.02	2,387 (6.9)	2,388 (7.0)	0.00
Influenza vaccine	4,118 (15.1)	1,249 (17.2)	0.06	5,382 (15.6)	5,343 (15.6)	0.00
Hemoglobin A1C test	14,505 (53.2)	4,349 (59.7)	0.13	18,858 (54.6)	18,631 (54.4)	0.00
Creatinine test	1,883 (6.9)	469 (6.4)	0.02	2,354 (6.8)	2,377 (6.9)	0.00
Comprehensive metabolic panel	14,472 (53.1)	4,338 (59.6)	0.13	18,833 (54.5)	18,773 (54.8)	0.01
Thyroid function test	8,465 (31.1)	2,509 (34.5)	0.07	11,001 (31.8)	11,164 (32.6)	0.02
Transthoracic echocardiogram	6,618 (24.3)	1,331 (18.3)	0.15	7,963 (23.1)	8,036 (23.5)	0.01

SD: standard deviation; SMD: standardized mean difference; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention

Mortality rates and risks (at 1, 3, and 5 years) for the overall cohort and according to age group are displayed in **Table 36**. Mortality rates per 1,000 person-years were 8.7 for ages 55–64, 22.2 for ages 65–74, and 68.9 for ages ≥75.

Table 36. Summary of mortality risks per 100 and rates in the Optum cohort overall and according to age group

	Total N	Deaths	Person-Years	Rate per 1,000 Person-Years	Cumulative Risk / 100, 1 year (95% CI)	Cumulative Risk / 100, 3 years (95% CI)	Cumulative Risk / 100, 5 years (95% CI)
Overall	34,197	2,712	95,497	28.4	0.9 (0.8, 1.0)	3.3 (3.1, 3.5)	6.2 (5.9, 6.5)
Age 55–64	14,102	315	36,277	8.7	0.2 (0.1, 0.3)	0.9 (0.7, 1.1)	1.9 (1.6, 2.2)
Age 65–74	11,787	800	36,034	22.2	0.7 (0.5, 0.8)	2.7 (2.4, 3.0)	5.0 (4.5, 5.4)
Age 75+	8,308	1,597	23,185	68.9	2.4 (2.0, 2.7)	8.2 (7.5, 8.8)	14.4 (13.5, 15.4)

A total of 5,495 outcome events occurred over 86,629 person-years. Average follow-up time in the overall cohort was 3.16 years (3.21 years for ramipril users, 2.99 years for telmisartan users). Cumulative risk estimates were similar for both exposure groups (**Table 37**). For ramipril users, sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 7.2 (95% 6.9, 7.6) and 7.3 (7.0, 7.7) at year 1 (difference = 0.1), were 16.9 (16.3, 17.4) and 17.4 (16.8, 18.0) at year 3 (difference = 0.6), and were 24.2 (23.5, 25.0) and 25.5 (24.7, 26.3) at year 5 (difference = 1.3) (**Figure 30** and **Table 38**). For telmisartan users, sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 6.3 (5.5, 7.0) and 6.3 (5.5, 7.0) at year 1 (difference = 0.0), were 17.0 (15.5, 18.4) and 17.4 (15.9, 18.8) at year 3 (difference = 0.4), and were 23.5 (21.8, 25.2) and 24.4 (22.6, 26.2) at year 5 (difference = 0.9). Comparison of the risk differences from the cause-specific versus sub-distribution models in the overall cohort across the 5 years of follow-up did not result in absolute differences per 100 greater than 0.4 (**Table 37** and **Table 38**).

Table 37. Cumulative risks and risk differences per 100 (telmisartan versus ramipril) of composite comparing cause-specific versus sub-distribution risk of composite outcome in the Optum cohort at 1, 3, and 5 years

Risk Time	Treatment Group	Events	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
Sub-Distribution				
1 year	Ramipril	1,778	7.2 (6.9, 7.6)	−1.0 (−1.8, −0.2)
	Telmisartan	424	6.3 (5.5, 7.0)	
3 years	Ramipril	3,498	16.9 (16.3, 17.4)	0.1 (−1.5, 1.6)
	Telmisartan	887	17.0 (15.5, 18.4)	
5 years	Ramipril	4,394	24.2 (23.5, 25.0)	−0.7 (−2.7, 1.2)
	Telmisartan	1,101	23.5 (21.8, 25.2)	
Cause-Specific				
1 year	Ramipril	1,778	7.3 (7.0, 7.7)	−1.0 (−1.9, −0.2)
	Telmisartan	424	6.3 (5.5, 7.0)	
3 years	Ramipril	3,498	17.4 (16.8, 18.0)	−0.1 (−1.7, 1.5)
	Telmisartan	887	17.4 (15.9, 18.8)	
5 years	Ramipril	4,394	25.5 (24.7, 26.3)	−1.1 (−3.1, 0.9)
	Telmisartan	1,101	24.4 (22.6, 26.2)	

Figure 30. Cumulative risk estimates from the sub-distribution and cause-specific models in the Optum cohort

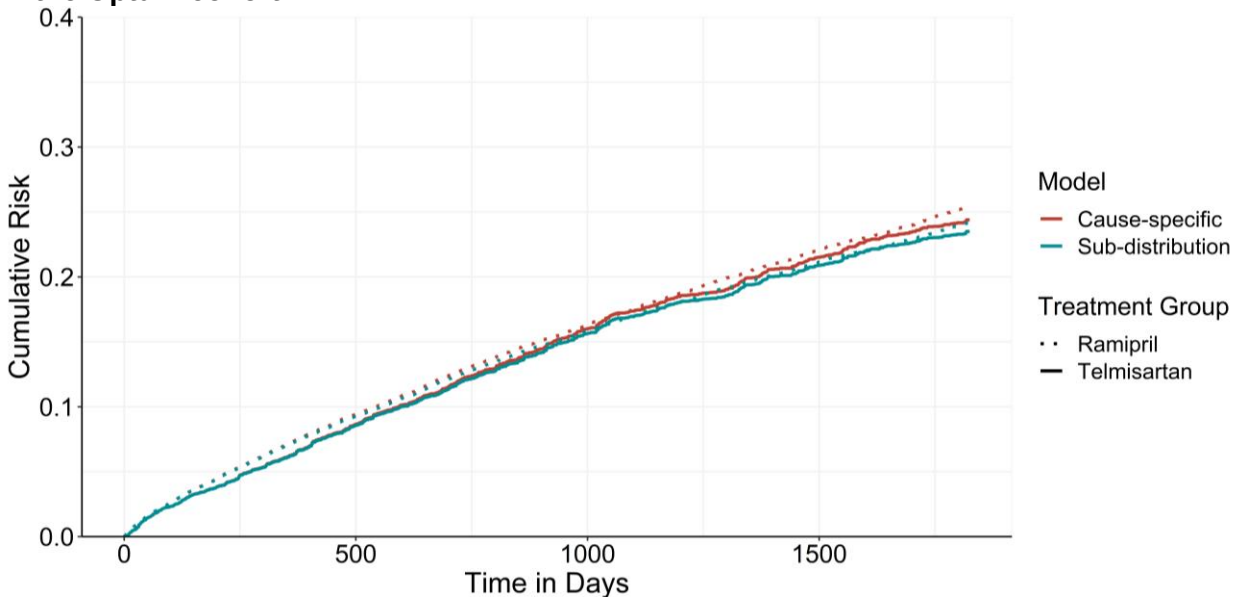


Table 38. Difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific versus sub-distribution risk of composite outcome in the Optum cohort at 1, 3, and 5 years

Risk Time	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
1 year	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.0 (0.0, 0.0)	
3 years	Ramipril	0.6 (0.6, 0.6)	−0.1 (−0.2, −0.1)
	Telmisartan	0.4 (0.4, 0.4)	
5 years	Ramipril	1.3 (1.3, 1.3)	−0.4 (−0.4, −0.4)
	Telmisartan	0.9 (0.9, 0.9)	

Cumulative risk estimates and risk difference estimates at 1, 3, and 5 years from sub-distribution and cause-specific models are displayed according to age category in **Table 39** and **Figure 31**. The increase in the difference in cumulative risks over time was greatest for the oldest age group (**Table 40** and **Figure 32**). Among ramipril users, 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 16.2 (15.1, 17.3) and 16.4 (15.3, 17.5) among ages 55–64 (difference = 0.2) and were 39.7 (37.9, 41.4) and 43.2 (41.3, 45.2) among ages ≥75 (difference = 3.6). Differences in the risk differences per 100 from the cause-specific versus sub-distribution models across the 5 years of follow-up did not exceed an absolute value of 1.0, even in the oldest age group (**Table 40** and **Figure 33**).

Table 39. Cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the Optum cohort by age category

Age Group	Treatment Group	Events	Sub-Distribution		Cause-Specific	
			Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
1 Year						
55–64	Ramipril	453	4.5 (4.1, 4.9)	−1.0 (−2.1, −0.0)	4.5 (4.1, 5.0)	−1.0 (−2.1, −0.0)
	Telmisartan	87	3.5 (2.6, 4.4)		3.5 (2.6, 4.4)	
65–74	Ramipril	580	6.8 (6.2, 7.3)	−0.4 (−2.0, 1.2)	6.8 (6.3, 7.4)	−0.4 (−2.0, 1.2)
	Telmisartan	146	6.4 (4.9, 7.9)		6.4 (5.0, 7.9)	
75+	Ramipril	745	13.0 (12.1, 14.0)	−2.8 (−4.8, −0.9)	13.3 (12.4, 14.3)	−3.0 (−5.0, −1.1)
	Telmisartan	191	10.2 (8.5, 11.9)		10.3 (8.6, 12.0)	
3 Years						
55–64	Ramipril	857	10.7 (10.0, 11.5)	−0.1 (−2.5, 2.3)	10.8 (10.1, 11.6)	−0.1 (−2.5, 2.3)
	Telmisartan	176	10.6 (8.4, 12.8)		10.7 (8.5, 13.0)	
65–74	Ramipril	1,176	16.3 (15.3, 17.2)	1.3 (−1.4, 3.9)	16.7 (15.7, 17.7)	1.2 (−1.5, 3.9)
	Telmisartan	332	17.6 (15.2, 20.0)		17.9 (15.4, 20.3)	
75+	Ramipril	1,465	29.1 (27.7, 30.6)	−2.5 (−6.2, 1.2)	30.6 (29.1, 32.2)	−2.7 (−6.6, 1.3)
	Telmisartan	379	26.7 (23.4, 30.0)		28.0 (24.5, 31.5)	
5 Years						
55–64	Ramipril	1,047	16.2 (15.1, 17.3)	−1.1 (−4.0, 1.8)	16.4 (15.3, 17.5)	−1.1 (−4.0, 1.8)
	Telmisartan	223	15.1 (12.5, 17.7)		15.3 (12.6, 18.0)	
65–74	Ramipril	1,512	23.8 (22.5, 25.0)	−0.0 (−3.2, 3.2)	24.7 (23.4, 26.0)	−0.4 (−3.7, 2.9)
	Telmisartan	406	23.8 (20.9, 26.7)		24.3 (21.3, 27.3)	
75+	Ramipril	1,465	39.7 (37.9, 41.4)	−3.0 (−7.7, 1.6)	43.2 (41.3, 45.2)	−3.9 (−9.0, 1.1)
	Telmisartan	379	36.6 (32.5, 40.8)		39.3 (34.8, 43.8)	

Figure 31. Cumulative risk estimates from the sub-distribution and cause-specific models in the Optum cohort by age category

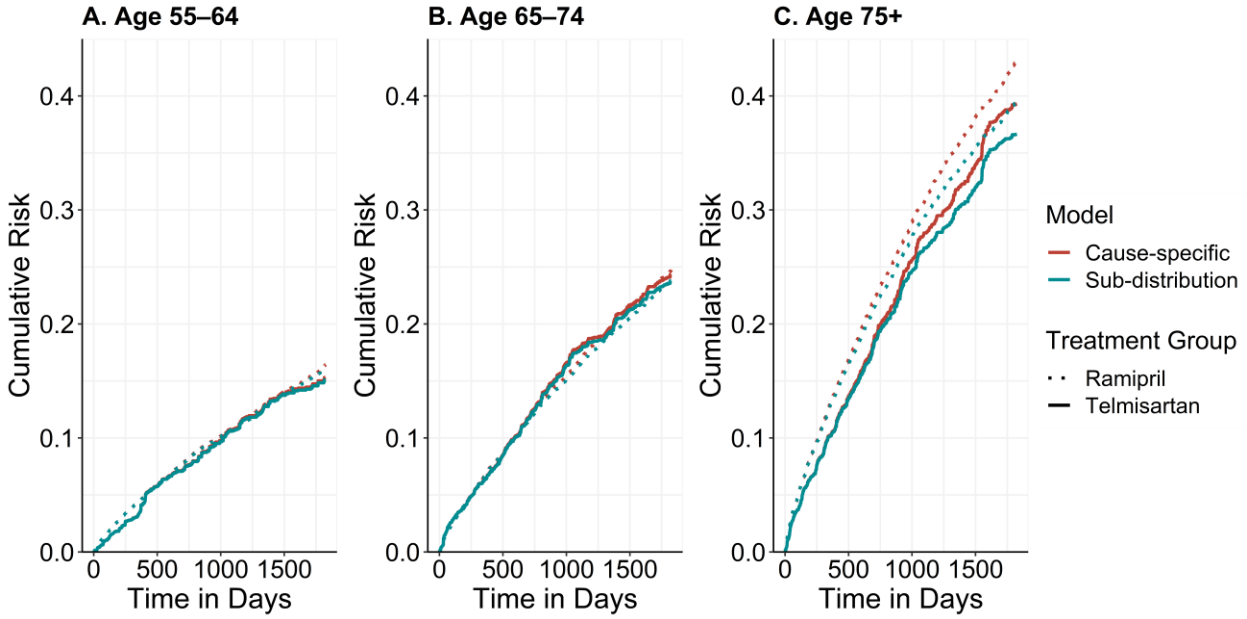


Table 40. Difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the Optum cohort at 1, 3, and 5 years by age category

Age Group	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
1 Year			
55–64	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	Telmisartan	0.0 (0.0, 0.0)	
65–74	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.0 (0.0, 0.0)	
75+	Ramipril	0.3 (0.3, 0.3)	−0.2 (−0.2, −0.2)
	Telmisartan	0.1 (0.1, 0.1)	
3 Years			
55–64	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.1 (0.1, 0.1)	
65–74	Ramipril	0.4 (0.4, 0.4)	−0.1 (−0.1, −0.1)
	Telmisartan	0.3 (0.3, 0.3)	
75+	Ramipril	1.5 (1.5, 1.5)	−0.2 (−0.2, −0.2)
	Telmisartan	1.3 (1.3, 1.3)	
5 Years			
55–64	Ramipril	0.2 (0.2, 0.2)	0.0 (0.0, 0.0)
	Telmisartan	0.2 (0.2, 0.2)	
65–74	Ramipril	0.9 (0.9. 0.9)	−0.4 (−0.4, −0.4)
	Telmisartan	0.6 (0.6, 0.6)	
75+	Ramipril	3.6 (3.6, 3.6)	−0.9 (−1.0, −0.9)
	Telmisartan	2.6 (2.6, 2.7)	

Figure 32. Difference in cumulative risks per 100 of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the Optum cohort, according to treatment category and age group

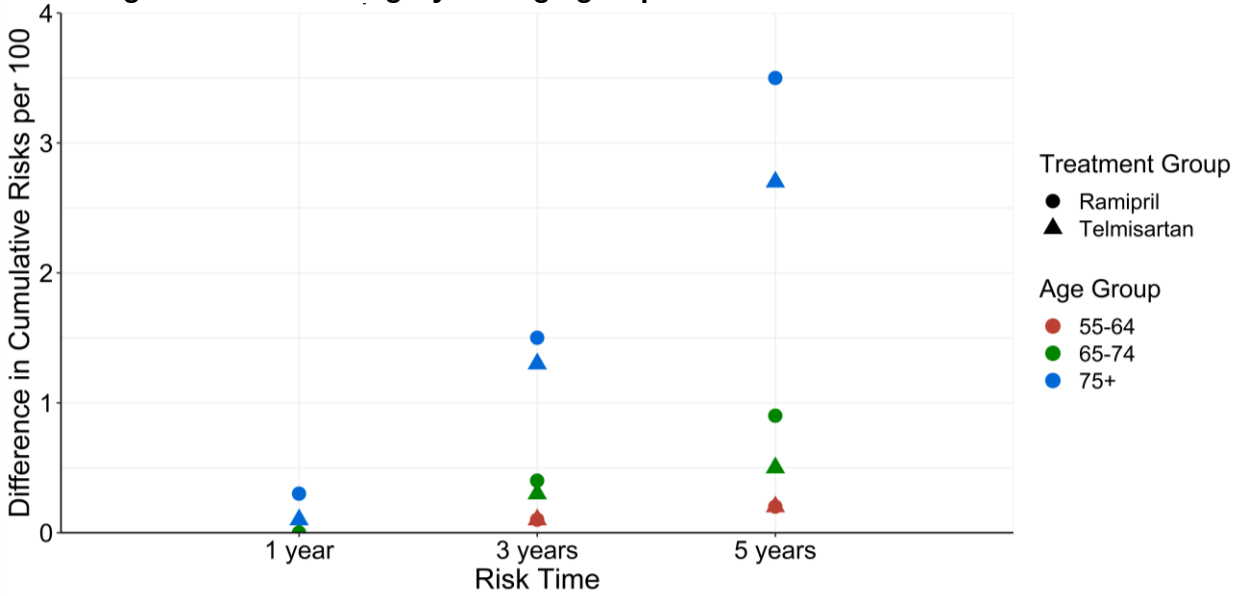
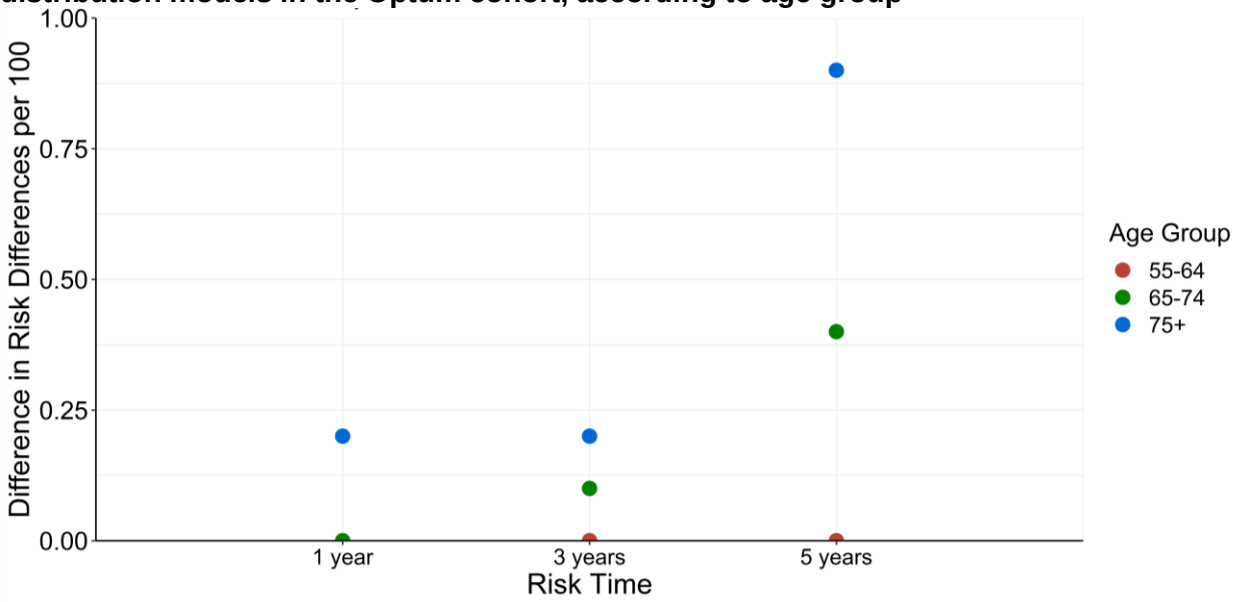


Figure 33. Absolute difference in risk differences per 100 (telmisartan versus ramipril) of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the Optum cohort, according to age group



Simple Simulation

The average overall and age-stratified mortality rates and risks from the baseline fully synthetically simulated cohorts, and under the doubling and tripling of the mortality rates, are displayed in **Table 41**.

Table 41. Summary of average mortality risks per 100 and rates in the fully synthetic simulated cohorts overall and according to age group

Mortality Rate	Rate per 1,000 Person-Years (95% CI)	Cumulative Risk / 100, 1 year (95% CI)	Cumulative Risk / 100, 3 years (95% CI)	Cumulative Risk / 100, 5 years (95% CI)
Overall				
Baseline	32.1 (31.5, 32.8)	2.3 (2.2, 2.4)	8.7 (8.5, 8.9)	16.0 (15.7, 16.3)
Double	60.7 (59.8, 61.6)	4.5 (4.3, 4.6)	16.2 (15.9, 16.4)	28.0 (27.6, 28.4)
Triple	86.5 (85.4, 87.7)	6.6 (6.4, 6.7)	22.6 (22.3, 22.9)	37.2 (36.8, 37.6)
Age 55–64				
Baseline	8.8 (8.2, 9.4)	0.7 (0.6, 0.7)	2.5 (2.3, 2.7)	4.7 (4.4, 5.0)
Double	17.6 (16.7, 18.4)	1.3 (1.2, 1.4)	5.0 (4.7, 5.3)	9.2 (8.7, 9.6)
Triple	26.3 (25.3, 27.3)	2.0 (1.8, 2.1)	7.4 (7.1, 7.8)	13.5 (12.9, 14.0)
Age 65–74				
Baseline	25.4 (24.5, 26.4)	1.9 (1.7, 2.0)	7.0 (6.6, 7.3)	12.6 (12.2, 13.1)
Double	50.4 (49.0, 51.8)	3.7 (3.5, 3.9)	13.4 (13.0, 13.8)	23.7 (23.1, 24.3)
Triple	75.1 (73.4, 76.7)	5.5 (5.2, 5.7)	19.4 (19.0, 19.9)	33.3 (32.6, 34.0)
Age 75+				
Baseline	78.5 (76.5, 80.5)	5.6 (5.3, 5.9)	20.0 (19.4, 20.6)	34.2 (33.5, 35.0)
Double	153.4 (150.5, 156.3)	10.9 (10.5, 11.3)	36.0 (35.3, 36.7)	56.7 (55.9, 57.5)
Triple	225.2 (221.3, 229.1)	15.9 (15.4, 16.5)	48.9 (48.1, 49.6)	71.5 (70.8, 72.3)

The average cumulative risk estimates and risk difference estimates at 1, 3, and 5 years from sub-distribution and cause-specific models from the fully synthetically simulated cohorts under baseline, doubling, and tripling of the mortality rate are displayed in **Table 42** and **Figure 34**. As expected, the difference in cumulative risks increased with the increasing mortality rate, such that the difference was greatest when the mortality rate was tripled (**Table 43** and **Figure 35**). For ramipril users, at year 5 the average cause-specific and sub-distribution risks per 100 were, respectively, 26.0 (25.5, 26.4) and 23.9 (23.5, 24.3) under the baseline mortality rate (difference = 2.1) and were 25.9 (25.4, 26.4) and 20.8 (20.4, 21.2) under the tripled mortality rate (difference = 5.1). The average difference in the risk differences per 100 from the cause-specific versus sub-distribution models across the 5 years of follow-up did not exceed an absolute value of 0.7, even when the mortality rate was tripled (**Table 43** and **Figure 36**).

Table 42. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts by mortality rate manipulation

Mortality Rate	Treatment Group	Sub-Distribution		Cause-Specific	
		Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
1 Year					
Baseline	Ramipril	6.9 (6.7, 7.1)	−0.5 (−0.8, −0.1)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.4 (6.1, 6.8)		6.5 (6.2, 6.9)	
Double	Ramipril	6.8 (6.6, 7.0)	−0.4 (−0.8, −0.1)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.4 (6.0, 6.7)		6.5 (6.2, 6.9)	
Triple	Ramipril	6.7 (6.5, 6.9)	−0.4 (−0.8, 0.0)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.3 (6.0, 6.6)		6.5 (6.2, 6.9)	
3 Years					
Baseline	Ramipril	16.7 (16.3, 17.0)	−1.0 (−1.6, −0.3)	17.5 (17.2, 17.8)	−1.1 (−1.8, −0.4)
	Telmisartan	15.7 (15.2, 16.3)		16.4 (15.8, 17.0)	
Double	Ramipril	15.9 (15.6, 16.2)	−0.8 (−1.5, −0.2)	17.5 (17.2, 17.9)	−1.1 (−1.8, −0.4)
	Telmisartan	15.1 (14.6, 15.6)		16.4 (15.8, 17.0)	
Triple	Ramipril	15.3 (15.0, 15.6)	−0.7 (−1.4, −0.1)	17.6 (17.2, 17.9)	−1.1 (−1.8, −0.4)
	Telmisartan	14.5 (14.0, 15.1)		16.4 (15.8, 17.0)	
5 Years					
Baseline	Ramipril	23.9 (23.5, 24.3)	−1.2 (−2.0, −0.3)	26.0 (25.5, 26.4)	−1.5 (−2.4, −0.6)
	Telmisartan	22.7 (22.0, 23.4)		24.4 (23.7, 25.2)	
Double	Ramipril	22.2 (21.8, 22.6)	−0.9 (−1.8, −0.1)	25.9 (25.5, 26.4)	−1.5 (−2.5, −0.6)
	Telmisartan	21.3 (20.5, 22.0)		24.4 (23.6, 25.3)	
Triple	Ramipril	20.8 (20.4, 21.2)	−0.8 (−1.6, 0.1)	25.9 (25.4, 26.4)	−1.5 (−2.6, −0.5)
	Telmisartan	20.0 (19.3, 20.7)		24.4 (23.5, 25.2)	

Figure 34. Average cumulative risk estimates of the composite outcome from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts under manipulations of the mortality rate

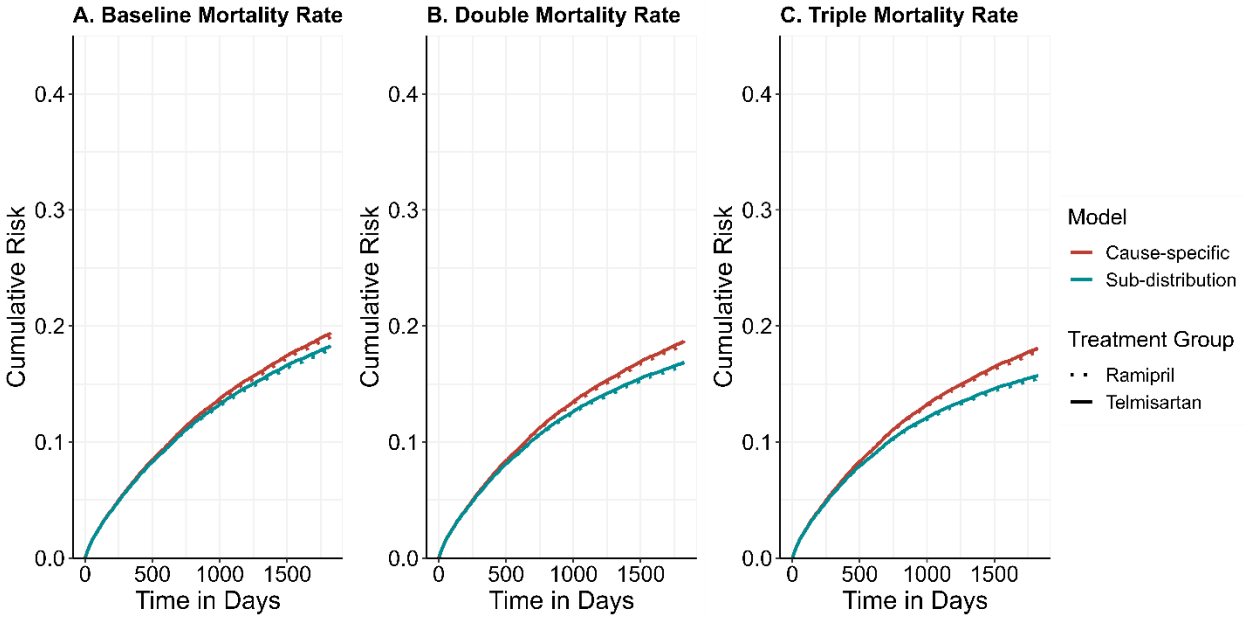


Table 43. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the fully synthetically simulated cohorts at 1, 3, and 5 years by mortality rate manipulation

Mortality Rate	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
1 Year			
Baseline	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.1 (0.1, 0.1)	
Double	Ramipril	0.2 (0.2, 0.2)	0.0 (−0.1, 0.0)
	Telmisartan	0.2 (0.2, 0.2)	
Triple	Ramipril	0.3 (0.3, 0.3)	−0.1 (−0.1, 0.0)
	Telmisartan	0.2 (0.2, 0.3)	
3 Years			
Baseline	Ramipril	0.9 (0.8, 0.9)	−0.2 (−0.2, −0.1)
	Telmisartan	0.7 (0.6, 0.8)	
Double	Ramipril	1.6 (1.5, 1.7)	−0.3 (−0.4, −0.2)
	Telmisartan	1.3 (1.2, 1.4)	
Triple	Ramipril	2.3 (2.2, 2.4)	−0.4 (−0.5, −0.2)
	Telmisartan	1.9 (1.8, 2.0)	
5 Years			
Baseline	Ramipril	2.1 (2.0, 2.2)	−0.3 (−0.5, −0.2)
	Telmisartan	1.7 (1.6, 1.9)	
Double	Ramipril	3.7 (3.6, 3.9)	−0.6 (−0.8, −0.3)
	Telmisartan	3.2 (3.0, 3.4)	
Triple	Ramipril	5.1 (4.9, 5.3)	−0.7 (−1.1, −0.4)
	Telmisartan	4.4 (4.1, 4.7)	

Figure 35. Average difference in cumulative risk estimates per 100 of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the fully synthetically simulated cohorts under manipulations of the mortality rate, according to treatment category

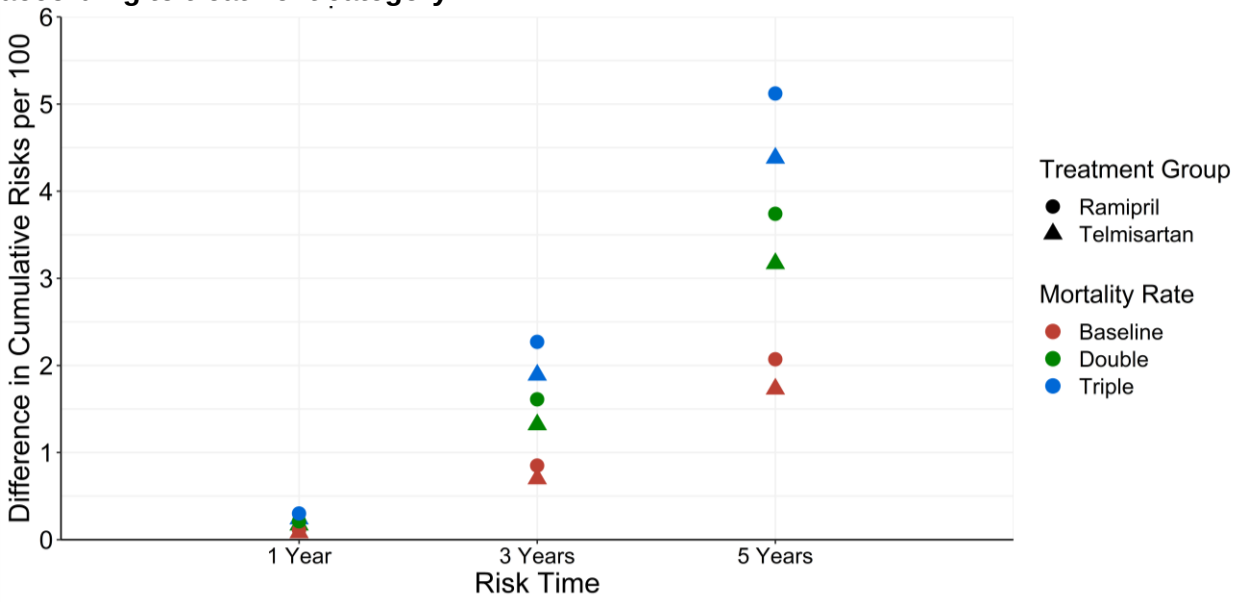
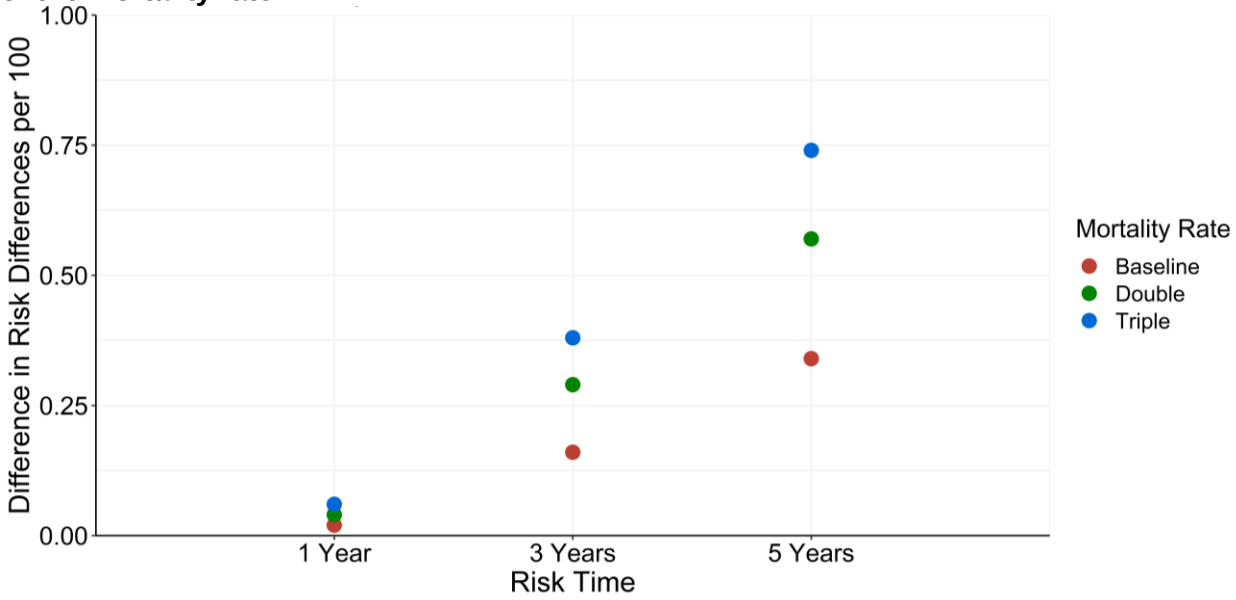


Figure 36. Average difference in risk difference estimates per 100 (telmisartan versus ramipril) of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the fully synthetically simulated cohorts under manipulations of the mortality rate



The average age-stratified cumulative risk estimates from the cause-specific and sub-distribution models given the baseline, double, and triple mortality rates are displayed in **Table 44** and **Figure 37**. In the youngest age group, where the baseline mortality rate was the lowest, tripling of the mortality rate (which resulted in a mortality rate similar to that of the baseline mortality rate in the 65–74 age group) did not produce substantial differences in the cause-specific versus sub-distribution risks. Among ramipril users age 55–65, the average 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 15.6 (15.0, 16.2) and 16.5 (15.9, 17.2) under the tripled mortality rate (difference = 1.0). The largest differences in response to the doubling and tripling of the mortality rate were observed in the oldest age group, for which the baseline mortality rate was even greater than the tripled mortality rates of the other groups (**Table 41**). Among ramipril users age 75+, the average 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 37.3 (36.4, 38.2) and 43.5 (42.5, 44.6) under the baseline mortality rate (difference = 6.2), were 32.5 (31.6, 33.3) and 43.5 (42.3, 44.8) under the doubled mortality rate (difference = 11.1), and were 28.6 (27.8, 29.4) and 43.6 (42.2, 45.0) under the tripled mortality rate (difference = 14.9). The largest average age-stratified difference in the risk differences per 100 from the cause-specific versus sub-distribution models under the doubling and tripling of the mortality rates was an absolute value of 2.0, which occurred in the oldest age group (**Table 45**).

Figure 37. Average cumulative risk estimates of the composite outcome from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts under manipulations of the mortality rate and according to age strata

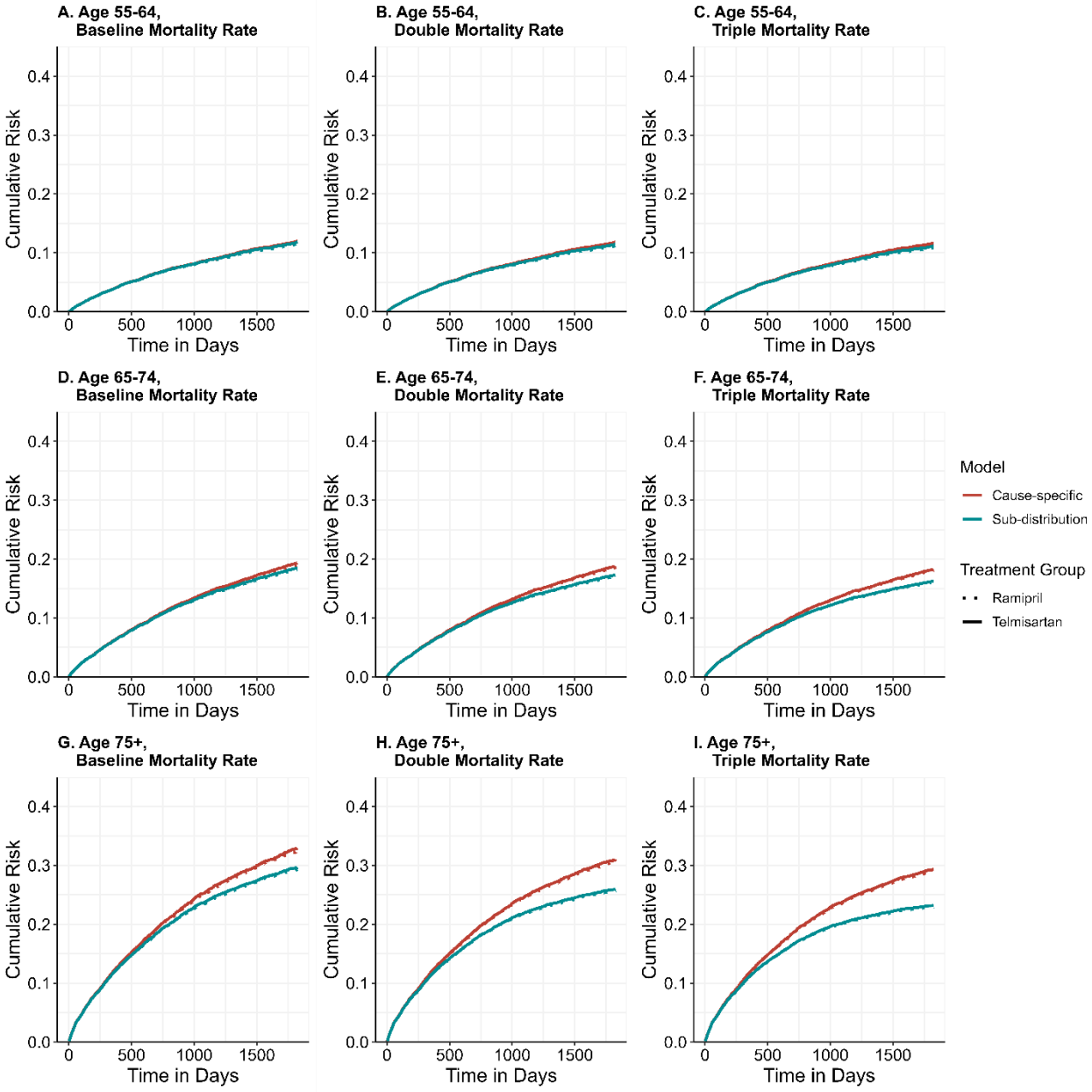


Table 44. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts by mortality rate manipulation

Risk Time	Mortality Rate	Treatment Group	Sub-Distribution		Cause-Specific	
			Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
Age 55−64						
1 year	Baseline	Ramipril	4.2 (3.9, 4.4)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4)	−0.3 (−0.8, 0.2)
		Telmisartan	3.9 (3.4, 4.3)		3.9 (3.4, 4.3)	
	Double	Ramipril	4.1 (3.9, 4.4)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4)	−0.3 (−0.8, 0.2)
		Telmisartan	3.9 (3.4, 4.3)		3.9 (3.4, 4.3)	
	Triple	Ramipril	4.1 (3.9, 4.4)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4)	−0.3 (−0.8, 0.2)
		Telmisartan	3.8 (3.4, 4.3)		3.9 (3.4, 4.3)	
3 years	Baseline	Ramipril	10.7 (10.2, 11.1)	−0.7 (−1.7, 0.3)	10.8 (10.3, 11.2)	−0.7 (−1.7, 0.3)
		Telmisartan	10.0 (9.2, 10.8)		10.1 (9.2, 10.9)	
	Double	Ramipril	10.6 (10.1, 11.0)	−0.7 (−1.6, 0.3)	10.8 (10.3, 11.2)	−0.7 (−1.7, 0.3)
		Telmisartan	9.9 (9.1, 10.7)		10.1 (9.2, 10.9)	
	Triple	Ramipril	10.5 (10.0, 10.9)	−0.7 (−1.6, 0.3)	10.8 (10.4, 11.2)	−0.7 (−1.7, 0.2)
		Telmisartan	9.8 (9.0, 10.6)		10.1 (9.2, 10.9)	
5 years	Baseline	Ramipril	16.2 (15.6, 16.8)	−1.0 (−2.4, 0.4)	16.5 (15.9, 17.2)	−1.0 (−2.4, 0.4)
		Telmisartan	15.2 (14.0, 16.5)		15.5 (14.3, 16.8)	
	Double	Ramipril	15.9 (15.3, 16.5)	−0.9 (−2.3, 0.5)	16.5 (15.9, 17.2)	−1.0 (−2.5, 0.4)
		Telmisartan	15.0 (13.8, 16.2)		15.5 (14.2, 16.8)	
	Triple	Ramipril	15.6 (15.0, 16.2)	−0.9 (−2.2, 0.5)	16.5 (15.9, 17.2)	−1.1 (−2.5, 0.4)
		Telmisartan	14.7 (13.5, 15.9)		15.5 (14.2, 16.8)	
Age 65−74						
1 year	Baseline	Ramipril	6.7 (6.4, 7.0)	−0.5 (−1.1, 0.2)	6.7 (6.4, 7.1)	−0.5 (−1.1, 0.2)
		Telmisartan	6.2 (5.7, 6.8)		6.3 (5.7, 6.8)	
	Double	Ramipril	6.6 (6.3, 6.9)	−0.4 (−1.1, 0.2)	6.7 (6.4, 7.1)	−0.5 (−1.1, 0.2)
		Telmisartan	6.2 (5.6, 6.7)		6.3 (5.7, 6.8)	
	Triple	Ramipril	6.6 (6.3, 6.9)	−0.4 (−1.0, 0.2)	6.7 (6.4, 7.1)	−0.4 (−1.1, 0.2)
		Telmisartan	6.2 (5.6, 6.7)		6.3 (5.8, 6.8)	
3 years	Baseline	Ramipril	16.6 (16.0, 17.1)	−1.0 (−2.1, 0.1)	17.1 (16.5, 17.6)	−1.1 (−2.2, 0.0)
		Telmisartan	15.6 (14.6, 16.5)		16.0 (15.0, 16.9)	
	Double	Ramipril	16.1 (15.6, 16.6)	−0.9 (−2.0, 0.2)	17.1 (16.5, 17.6)	−1.1 (−2.2, 0.0)
		Telmisartan	15.2 (14.2, 16.1)		16.0 (15.0, 17.0)	
	Triple	Ramipril	15.6 (15.1, 16.1)	−0.8 (−1.9, 0.2)	17.1 (16.5, 17.6)	−1.1 (−2.2, 0.0)
		Telmisartan	14.8 (13.9, 15.6)		16.0 (15.0, 16.9)	
5 years	Baseline	Ramipril	24.3 (23.6, 24.9)	−1.3 (−2.7, 0.1)	25.6 (24.9, 26.4)	−1.6 (−3.0, −0.1)
		Telmisartan	23.0 (21.7, 24.2)		24.1 (22.8, 25.4)	
	Double	Ramipril	23.0 (22.4, 23.7)	−1.1 (−2.5, 0.3)	25.6 (24.9, 26.4)	−1.6 (−3.1, 0.0)
		Telmisartan	21.9 (20.7, 23.1)		24.1 (22.8, 25.4)	
	Triple	Ramipril	21.9 (21.3, 22.5)	−0.9 (−2.2, 0.3)	25.7 (24.9, 26.4)	−1.6 (−3.1, 0.0)
		Telmisartan	21.0 (19.9, 22.0)		24.1 (22.8, 25.4)	
Age 75+						
1 year	Baseline	Ramipril	12.3 (11.8, 12.8)	−0.8 (−1.7, 0.2)	12.6 (12.0, 13.1)	−0.8 (−1.8, 0.1)
		Telmisartan	11.5 (10.7, 12.3)		11.7 (10.9, 12.6)	
	Double	Ramipril	12.0 (11.5, 12.5)	−0.7 (−1.7, 0.2)	12.6 (12.0, 13.1)	−0.8 (−1.8, 0.2)
		Telmisartan	11.2 (10.4, 12.0)		11.7 (10.9, 12.6)	
	Triple	Ramipril	11.7 (11.2, 12.2)	−0.7 (−1.6, 0.3)	12.6 (12.0, 13.1)	−0.8 (−1.9, 0.2)
		Telmisartan	11.0 (10.2, 11.9)		11.7 (10.9, 12.6)	
3 years	Baseline	Ramipril	27.7 (27.0, 28.5)	−1.4 (−2.8, 0.1)	30.3 (29.5, 31.1)	−1.8 (−3.4, −0.2)
		Telmisartan	26.4 (25.1, 27.6)		28.5 (27.1, 29.8)	
	Double	Ramipril	25.5 (24.8, 26.2)	−1.0 (−2.4, 0.4)	30.3 (29.5, 31.2)	−1.8 (−3.5, −0.2)
		Telmisartan	24.5 (23.3, 25.7)		28.5 (27.1, 29.9)	
	Triple	Ramipril	23.6 (22.9, 24.3)	−0.8 (−2.1, 0.7)	30.3 (29.4, 31.2)	−1.8 (−3.6, 0.0)
		Telmisartan	22.8 (21.6, 24.0)		28.5 (27.0, 30.1)	
5 years	Baseline	Ramipril	37.3 (36.4, 38.2)	−1.3 (−3.1, 0.4)	43.5 (42.5, 44.6)	−2.3 (−4.4, −0.2)
		Telmisartan	36.0 (34.5, 37.5)		41.2 (39.4, 43.0)	
	Double	Ramipril	32.5 (31.6, 33.3)	−0.7 (−2.4, 0.9)	43.5 (42.3, 44.8)	−2.3 (−4.7, 0.0)
		Telmisartan	31.7 (30.3, 33.1)		41.2 (39.3, 43.1)	
	Triple	Ramipril	28.6 (27.8, 29.4)	−0.3 (−1.9, 1.2)	43.6 (42.2, 45.0)	−2.4 (−5.0, 0.2)
		Telmisartan	28.3 (26.9, 29.6)		41.2 (39.0, 43.3)	

Table 45. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the fully synthetically simulated cohorts at 1, 3, and 5 years by mortality rate manipulation, according to age strata

Risk Time	Mortality Rate	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
Age 55−64				
1 year	Baseline	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	Double	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	Triple	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
3 years	Baseline	Ramipril	0.1 (0.1, 0.1)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.1)	
	Double	Ramipril	0.2 (0.2, 0.3)	0.0 (−0.1, 0.0)
		Telmisartan	0.2 (0.2, 0.2)	
	Triple	Ramipril	0.3 (0.3, 0.4)	−0.1 (−0.1, 0.0)
		Telmisartan	0.3 (0.2, 0.3)	
5 years	Baseline	Ramipril	0.3 (0.3, 0.4)	−0.1 (−0.1, 0.0)
		Telmisartan	0.3 (0.2, 0.3)	
	Double	Ramipril	0.6 (0.6, 0.7)	−0.1 (−0.2, 0.0)
		Telmisartan	0.5 (0.4, 0.6)	
	Triple	Ramipril	1.0 (0.9, 1.0)	−0.2 (−0.3, 0.0)
		Telmisartan	0.8 (0.7, 0.9)	
Age 65−74				
1 year	Baseline	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.1)	
	Double	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
		Telmisartan	0.1 (0.1, 0.1)	
	Triple	Ramipril	0.2 (0.2, 0.2)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.2)	
3 years	Baseline	Ramipril	0.5 (0.5, 0.5)	−0.1 (−0.2, 0.0)
		Telmisartan	0.4 (0.4, 0.5)	
	Double	Ramipril	1.0 (0.9, 1.1)	−0.2 (−0.3, −0.1)
		Telmisartan	0.8 (0.7, 0.9)	
	Triple	Ramipril	1.5 (1.4, 1.5)	−0.3 (−0.4, −0.1)
		Telmisartan	1.2 (1.1, 1.3)	
5 years	Baseline	Ramipril	1.4 (1.3, 1.5)	−0.2 (−0.4, −0.1)
		Telmisartan	1.1 (1.0, 1.3)	
	Double	Ramipril	2.6 (2.5, 2.8)	−0.4 (−0.7, −0.2)
		Telmisartan	2.2 (1.9, 2.4)	
	Triple	Ramipril	3.8 (3.6, 4.0)	−0.6 (−1.0, −0.3)
		Telmisartan	3.1 (2.8, 3.5)	
Age 75+				
1 year	Baseline	Ramipril	0.3 (0.3, 0.3)	−0.1 (−0.1, 0.0)
		Telmisartan	0.3 (0.2, 0.3)	
	Double	Ramipril	0.6 (0.6, 0.6)	−0.1 (−0.2, 0.0)
		Telmisartan	0.5 (0.4, 0.6)	
	Triple	Ramipril	0.9 (0.8, 0.9)	−0.2 (−0.3, −0.1)
		Telmisartan	0.7 (0.6, 0.8)	
3 years	Baseline	Ramipril	2.6 (2.4, 2.7)	−0.4 (−0.7, −0.2)
		Telmisartan	2.1 (1.9, 2.3)	
	Double	Ramipril	4.8 (4.5, 5.1)	−0.8 (−1.2, −0.4)
		Telmisartan	4.0 (3.6, 4.4)	
	Triple	Ramipril	6.7 (6.4, 7.1)	−1.1 (−1.7, −0.4)
		Telmisartan	5.7 (5.2, 6.2)	
5 years	Baseline	Ramipril	6.2 (5.9, 6.5)	−1.0 (−1.6, −0.4)
		Telmisartan	5.3 (4.8, 5.7)	
	Double	Ramipril	11.1 (10.5, 11.6)	−1.6 (−2.6, −0.6)
		Telmisartan	9.5 (8.7, 10.3)	
	Triple	Ramipril	14.9 (14.1, 15.8)	−2.0 (−3.5, −0.6)
		Telmisartan	12.9 (11.7, 14.1)	

Plasmode Simulation

The average overall and age-stratified mortality rates and risks from the plasmode-simulated cohorts, under the baseline, doubled, and tripled mortality rates, are displayed in **Table 46**.

Table 46. Summary of average mortality risks per 100 and rates in the plasmode-simulated cohorts overall and according to age group

Mortality Rate	Rate per 1,000 Person-Years	Cumulative Risk / 100, 1 year (95% CI)	Cumulative Risk / 100, 3 years (95% CI)	Cumulative Risk / 100, 5 years (95% CI)
Overall				
Baseline	28.9 (27.9, 30.0)	1.8 (1.6, 1.9)	7.8 (7.5, 8.1)	15.0 (14.5, 15.6)
Double	52.4 (51.0, 53.9)	3.5 (3.3, 3.7)	14.0 (13.6, 14.5)	25.3 (24.6, 26.0)
Triple	72.9 (71.3, 74.8)	5.1 (4.8, 5.3)	19.3 (18.8, 19.9)	33.2 (32.4, 34.0)
Age 55–64				
Baseline	8.3 (7.3, 9.3)	0.5 (0.4, 0.6)	2.3 (2.0, 2.7)	4.7 (4.1, 5.3)
Double	16.3 (15.1, 17.6)	1.0 (0.9, 1.2)	4.5 (4.1, 5.0)	9.0 (8.3, 9.8)
Triple	24.1 (22.5, 25.8)	1.5 (1.3, 1.7)	6.7 (6.2, 7.3)	13.0 (12.2, 14.0)
Age 65–74				
Baseline	24.1 (22.6, 25.9)	1.5 (1.2, 1.7)	6.4 (5.9, 7.0)	12.5 (11.7, 13.3)
Double	46.2 (44.1, 48.7)	2.9 (2.6, 3.2)	12.1 (11.4, 12.9)	22.6 (21.6, 23.8)
Triple	66.9 (64.5, 70.0)	4.3 (3.9, 4.7)	17.3 (16.5, 18.2)	31.2 (30.2, 32.4)
Age 75+				
Baseline	70.4 (67.3, 73.9)	4.5 (4.1, 5.0)	18.1 (17.1, 19.1)	32.1 (30.8, 33.4)
Double	128.4 (123.7, 133.0)	8.6 (8.0, 9.3)	31.4 (30.2, 32.5)	50.9 (49.4, 52.4)
Triple	179.4 (174.0, 185.1)	12.5 (11.8, 13.3)	41.7 (40.5, 43.0)	63.2 (61.8, 64.6)

The average cumulative risk estimates and risk difference estimates at 1, 3, and 5 years from sub-distribution and cause-specific models in the plasmode cohorts under baseline, doubling, and tripling of the mortality rate are displayed in **Table 47** and **Figure 38**. As expected, doubling and tripling the mortality rate resulted in an increase in the difference in cumulative risks of the cause-specific versus sub-distribution model at 1, 3, and 5 years (**Table 48** and **Figure 39**). For ramipril users, at year 5 the average cause-specific and sub-distribution risks per 100 were, respectively, 19.1 (18.4, 19.8) and 18.0 (17.4, 18.7) under the baseline mortality rate (difference = 1.1) and were 17.8 (17.1, 18.6) and 15.5 (14.9, 16.2) under the tripled mortality rate (difference = 2.3). The average difference in the risk differences per 100 from the cause-specific versus sub-distribution models across the 5 years of follow-up did not exceed 0.0, even when the mortality rate was tripled (**Table 48** and **Figure 40**).

Table 47. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the plasmode-simulated cohorts by mortality rate manipulation

Mortality Rate	Treatment Group	Sub-Distribution		Cause-Specific	
		Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
1 Year					
Baseline	Ramipril	6.6 (6.2, 6.9)	0.0 (−0.7, 0.7)	6.7 (6.3, 7.0)	0.0 (−0.7, 0.7)
	Telmisartan	6.6 (5.9, 7.2)		6.7 (6.0, 7.3)	
Double	Ramipril	6.5 (6.1, 6.8)	0.0 (−0.7, 0.7)	6.6 (6.3, 7.0)	0.0 (−0.7, 0.7)
	Telmisartan	6.5 (5.8, 7.1)		6.6 (6.0, 7.3)	
Triple	Ramipril	6.4 (6.0, 6.7)	0.0 (−0.7, 0.7)	6.6 (6.2, 6.9)	0.0 (−0.7, 0.7)
	Telmisartan	6.4 (5.7, 7.0)		6.6 (5.9, 7.2)	
3 Years					
Baseline	Ramipril	13.8 (13.3, 14.3)	0.2 (−1.0, 1.3)	14.3 (13.8, 14.9)	0.2 (−1.0, 1.4)
	Telmisartan	14.0 (12.9, 15.0)		14.5 (13.4, 15.5)	
Double	Ramipril	13.1 (12.6, 13.6)	0.2 (−1.0, 1.2)	14.0 (13.5, 14.6)	0.2 (−1.1, 1.3)
	Telmisartan	13.3 (12.3, 14.2)		14.2 (13.1, 15.2)	
Triple	Ramipril	12.5 (12.0, 13.0)	0.2 (−1.0, 1.2)	13.8 (13.2, 14.4)	0.1 (−1.1, 1.3)
	Telmisartan	12.7 (11.7, 13.6)		13.9 (12.8, 14.9)	
5 Years					
Baseline	Ramipril	18.0 (17.4, 18.7)	0.3 (−1.1, 1.8)	19.1 (18.4, 19.8)	0.3 (−1.2, 1.9)
	Telmisartan	18.3 (17.1, 19.7)		19.4 (18.1, 21.0)	
Double	Ramipril	16.6 (16.0, 17.3)	0.3 (−1.1, 1.7)	18.4 (17.8, 19.2)	0.3 (−1.3, 1.9)
	Telmisartan	16.9 (15.6, 18.2)		18.7 (17.3, 20.2)	
Triple	Ramipril	15.5 (14.9, 16.2)	0.2 (−1.0, 1.6)	17.8 (17.1, 18.6)	0.3 (−1.3, 2.1)
	Telmisartan	15.7 (14.6, 17.0)		18.1 (16.7, 19.6)	

Figure 38. Average cumulative risk estimates of the composite outcome from the sub-distribution and cause-specific models in the plasmode-simulated cohorts under manipulations of the mortality rate

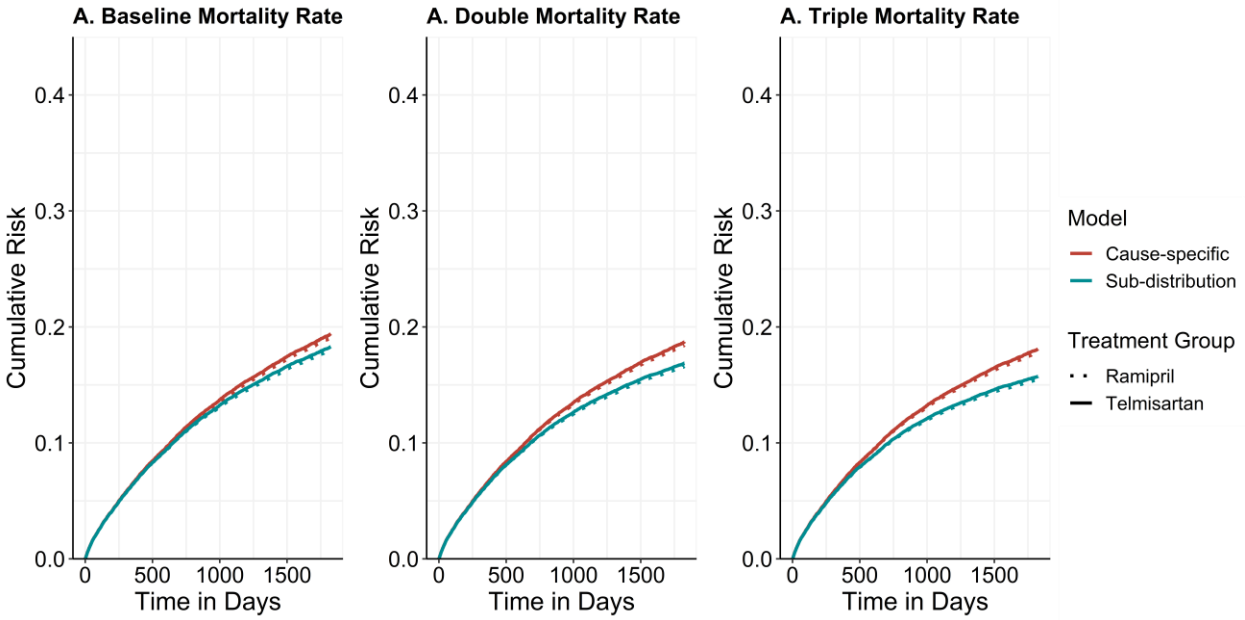


Table 48. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the plasmode-simulated cohorts at 1, 3, and 5 years by mortality rate manipulation

Mortality Rate	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
1 Year			
Baseline	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.1)
	Telmisartan	0.1 (0.1, 0.2)	
Double	Ramipril	0.2 (0.2, 0.2)	0.0 (−0.1, 0.1)
	Telmisartan	0.2 (0.1, 0.3)	
Triple	Ramipril	0.2 (0.2, 0.3)	0.0 (−0.1, 0.1)
	Telmisartan	0.2 (0.2, 0.3)	
3 Years			
Baseline	Ramipril	0.5 (0.5, 0.6)	0.0 (−0.1, 0.1)
	Telmisartan	0.5 (0.4, 0.7)	
Double	Ramipril	1.0 (0.9, 1.0)	0.0 (−0.2, 0.2)
	Telmisartan	0.9 (0.8, 1.1)	
Triple	Ramipril	1.3 (1.2, 1.4)	0.0 (−0.2, 0.3)
	Telmisartan	1.3 (1.1, 1.5)	
5 Years			
Baseline	Ramipril	1.1 (1.0, 1.2)	0.0 (−0.2, 0.3)
	Telmisartan	1.1 (0.9, 1.4)	
Double	Ramipril	1.8 (1.7, 2.0)	0.0 (−0.4, 0.5)
	Telmisartan	1.8 (1.5, 2.3)	
Triple	Ramipril	2.3 (2.1, 2.6)	0.0 (−0.5, 0.6)
	Telmisartan	2.3 (1.9, 2.9)	

Figure 39. Average difference in cumulative risk estimates per 100 of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the plasmode-simulated cohorts under manipulations of the mortality rate, according to treatment category

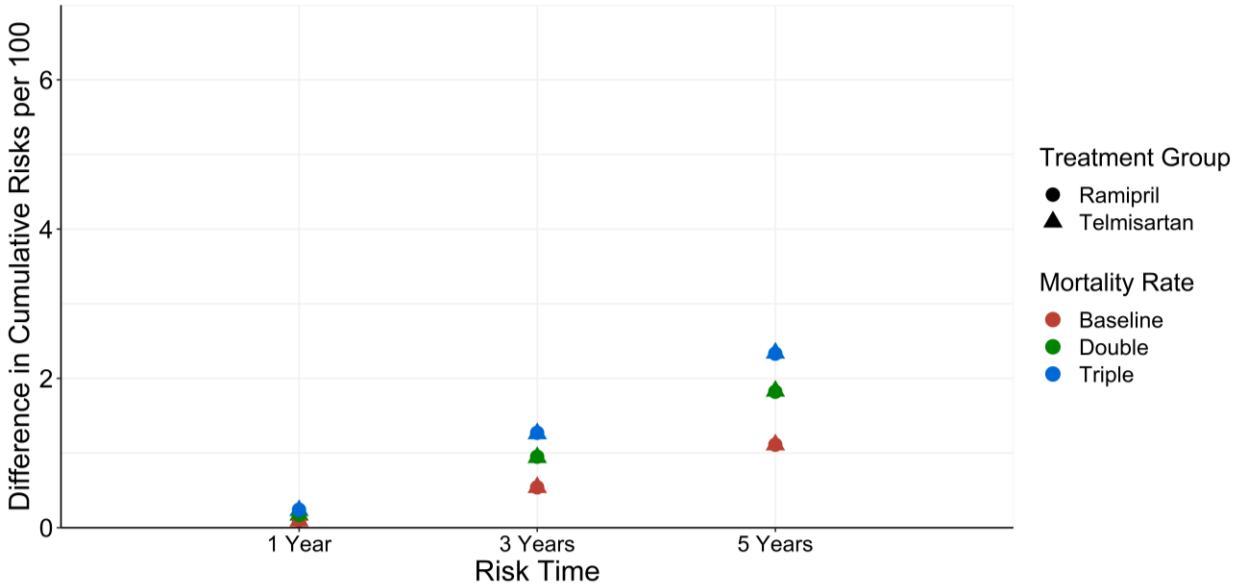
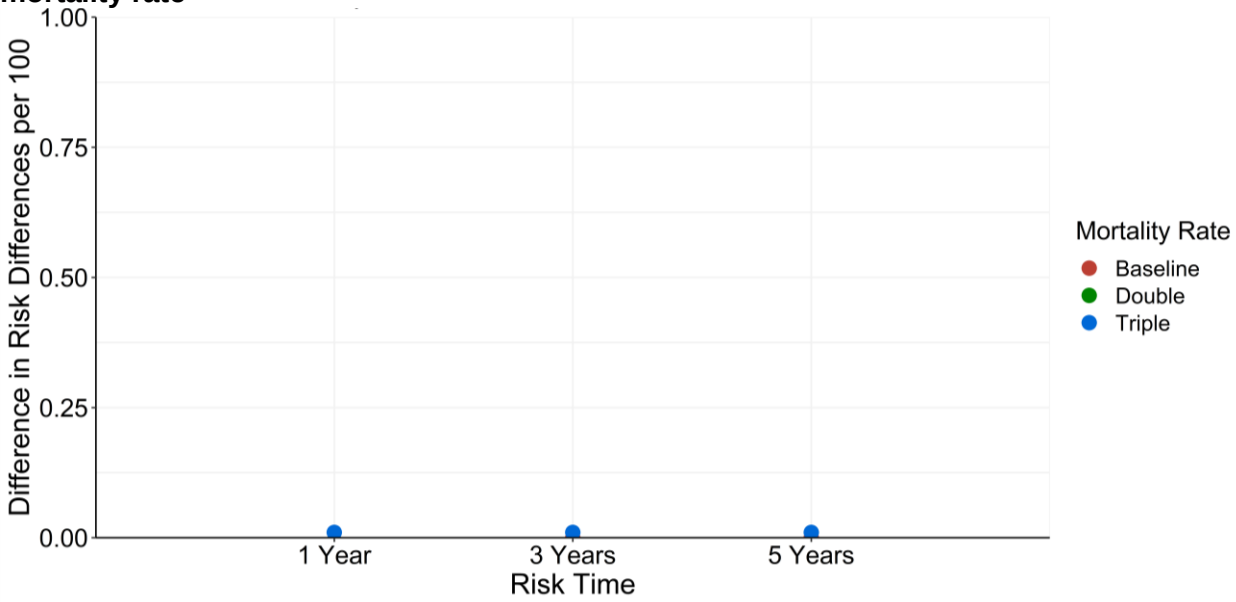


Figure 40. Average difference in risk difference estimates per 100 (telmisartan versus ramipril) of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the plasmode-simulated cohorts under manipulations of the mortality rate



The average age-stratified cumulative risk estimates from the cause-specific and sub-distribution models given the baseline, double, and triple mortality rates in the plasmode-simulated cohorts are displayed in **Table 49** and **Figure 41**. In the youngest age group, where the baseline mortality rate was the lowest, tripling of the mortality rate (which resulted in a mortality rate similar to that of the baseline mortality rate in the 65–74 age group) did not produce substantial differences in the cause-specific versus sub-distribution risks (**Table 50**). Among ramipril users age 55–65, the average 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 10.9 (10.1, 11.9) and 11.4 (10.5, 12.5) under the tripled mortality rate (difference = 0.5). The largest differences in response to the doubling and tripling of the mortality rate were observed in the oldest age group, for which the baseline mortality rate was even greater than the tripled mortality rates of the other groups (**Table 46**). Among ramipril users age 75+, the average 5-year sub-distribution and cause-specific cumulative risk estimates per 100, respectively, were 29.4 (27.8, 30.9) and 32.6 (30.6, 34.3) under the baseline mortality rate (difference = 3.2), were 25.7 (24.3, 27.2) and 30.7 (28.7,

32.7) under the doubled mortality rate (difference = 5.0), and were 23.0 (21.7, 24.4) and 29.0 (27.1, 31.1) under the tripled mortality rate (difference = 6.0). The largest average age-stratified difference in the risk differences per 100 from the cause-specific versus sub-distribution models under the doubling and tripling of the mortality rates was an absolute value of 0.1, which occurred in the oldest age group (**Table 50**).

Figure 41. Average cumulative risk estimates of the composite outcome from the sub-distribution and cause-specific models in the plasmode-simulated cohorts under manipulations of the mortality rate and according to age strata

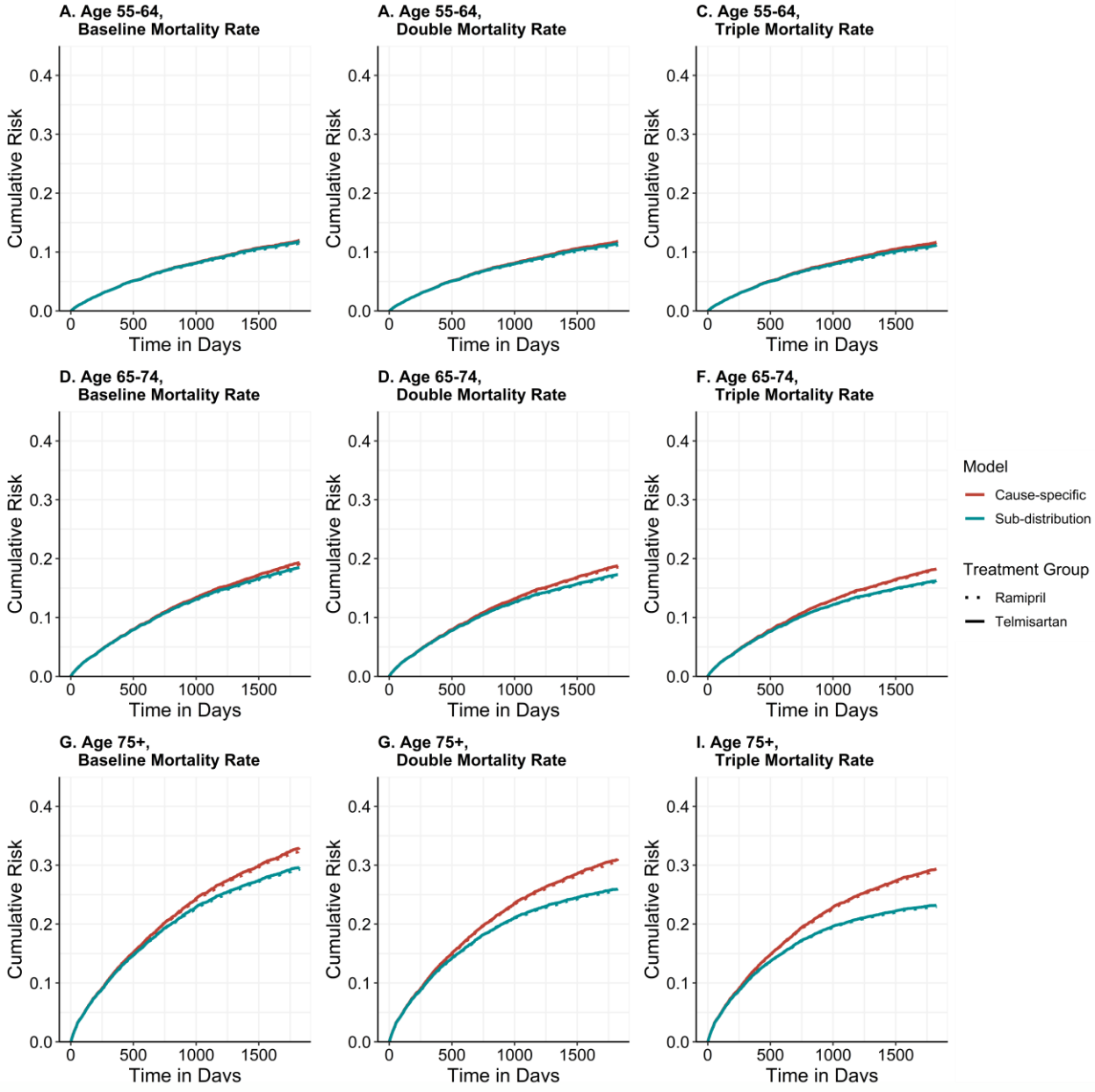


Table 49. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the plasmode-simulated cohorts by mortality rate manipulation

Risk Time	Mortality Rate	Treatment Group	Sub-Distribution		Cause-Specific	
			Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
Age 55−64						
1 year	Baseline	Ramipril	3.9 (3.6, 4.4)	0.0 (−0.9, 1.0)	4.0 (3.6, 4.4)	0.0 (−0.9, 1.0)
		Telmisartan	4.0 (3.1, 4.8)		4.0 (3.1, 4.9)	
	Double	Ramipril	3.9 (3.6, 4.3)	0.0 (−0.9, 1.0)	3.9 (3.6, 4.4)	0.0 (−0.9, 1.0)
		Telmisartan	3.9 (3.1, 4.8)		4.0 (3.1, 4.8)	
	Triple	Ramipril	3.9 (3.5, 4.3)	0.0 (−0.9, 1.0)	3.9 (3.6, 4.4)	0.0 (−0.9, 1.0)
		Telmisartan	3.9 (3.1, 4.8)		4.0 (3.1, 4.8)	
3 years	Baseline	Ramipril	8.5 (7.8, 9.2)	0.1 (−1.5, 1.8)	8.5 (7.9, 9.3)	0.1 (−1.5, 1.8)
		Telmisartan	8.6 (7.2, 10.2)		8.7 (7.3, 10.3)	
	Double	Ramipril	8.3 (7.7, 9.1)	0.1 (−1.4, 1.7)	8.5 (7.8, 9.2)	0.1 (−1.4, 1.8)
		Telmisartan	8.4 (7.1, 10.0)		8.6 (7.2, 10.2)	
	Triple	Ramipril	8.2 (7.5, 8.9)	0.1 (−1.4, 1.8)	8.4 (7.7, 9.2)	0.2 (−1.4, 1.9)
		Telmisartan	8.3 (7.0, 9.8)		8.6 (7.2, 10.1)	
5 years	Baseline	Ramipril	11.5 (10.7, 12.6)	0.3 (−1.9, 3.0)	11.7 (10.8, 12.8)	0.3 (−2.0, 3.0)
		Telmisartan	11.8 (10.0, 14.2)		12.0 (10.1, 14.4)	
	Double	Ramipril	11.2 (10.4, 12.2)	0.3 (−1.7, 2.8)	11.6 (10.6, 12.6)	0.3 (−1.9, 2.8)
		Telmisartan	11.5 (9.7, 13.8)		11.8 (9.9, 14.3)	
	Triple	Ramipril	10.9 (10.1, 11.9)	0.3 (−1.7, 2.7)	11.4 (10.5, 12.5)	0.3 (−1.8, 2.8)
		Telmisartan	11.2 (9.4, 13.4)		11.7 (9.8, 14.1)	
Age 65−74						
1 year	Baseline	Ramipril	6.2 (5.7, 6.8)	0.0 (−1.1, 1.2)	6.3 (5.7, 6.9)	0.0 (−1.1, 1.2)
		Telmisartan	6.2 (5.3, 7.3)		6.2 (5.3, 7.4)	
	Double	Ramipril	6.2 (5.6, 6.7)	0.0 (−1.1, 1.2)	6.3 (5.7, 6.8)	0.0 (−1.1, 1.2)
		Telmisartan	6.1 (5.2, 7.2)		6.2 (5.3, 7.4)	
	Triple	Ramipril	6.1 (5.5, 6.6)	0.0 (−1.1, 1.2)	6.2 (5.7, 6.8)	0.0 (−1.1, 1.2)
		Telmisartan	6.1 (5.1, 7.2)		6.2 (5.3, 7.3)	
3 years	Baseline	Ramipril	13.8 (12.9, 14.6)	0.1 (−1.6, 2.0)	14.1 (13.3, 15.0)	0.1 (−1.7, 2.2)
		Telmisartan	13.9 (12.4, 15.6)		14.3 (12.7, 16.0)	
	Double	Ramipril	13.2 (12.4, 14.1)	0.1 (−1.6, 2.0)	13.9 (13.0, 14.9)	0.1 (−1.8, 2.2)
		Telmisartan	13.3 (11.8, 15.0)		14.0 (12.5, 15.8)	
	Triple	Ramipril	12.7 (11.9, 13.6)	0.1 (−1.6, 2.0)	13.7 (12.8, 14.7)	0.1 (−1.8, 2.2)
		Telmisartan	12.8 (11.3, 14.4)		13.8 (12.2, 15.6)	
5 years	Baseline	Ramipril	18.2 (17.2, 19.4)	0.2 (−1.9, 2.8)	19.1 (17.9, 20.3)	0.2 (−2.0, 2.9)
		Telmisartan	18.5 (16.6, 20.7)		19.3 (17.3, 21.7)	
	Double	Ramipril	17.1 (16.1, 18.1)	0.2 (−1.9, 2.6)	18.6 (17.4, 19.7)	0.2 (−2.2, 3.0)
		Telmisartan	17.3 (15.4, 19.4)		18.8 (16.7, 21.2)	
	Triple	Ramipril	16.1 (15.0, 17.1)	0.1 (−1.8, 2.5)	18.1 (16.9, 19.3)	0.2 (−2.3, 2.8)
		Telmisartan	16.2 (14.4, 18.3)		18.2 (16.1, 20.7)	
Age 75+						
1 year	Baseline	Ramipril	11.9 (11.0, 12.8)	0.1 (−1.8, 1.9)	12.2 (11.3, 13.1)	0.1 (−1.9, 2.0)
		Telmisartan	11.9 (10.3, 13.6)		12.2 (10.5, 14.0)	
	Double	Ramipril	11.6 (10.7, 12.5)	0.1 (−1.8, 1.9)	12.1 (11.1, 13.1)	0.1 (−1.9, 2.0)
		Telmisartan	11.6 (10.0, 13.3)		12.2 (10.4, 13.9)	
	Triple	Ramipril	11.3 (10.4, 12.2)	0.1 (−1.8, 1.8)	12.0 (11.1, 13.0)	0.1 (−1.9, 2.0)
		Telmisartan	11.4 (9.7, 13.0)		12.0 (10.3, 13.8)	
3 years	Baseline	Ramipril	23.7 (22.4, 25.0)	0.2 (−2.4, 3.0)	25.3 (23.9, 26.7)	0.2 (−2.5, 3.3)
		Telmisartan	23.9 (21.4, 26.3)		25.5 (22.9, 28.3)	
	Double	Ramipril	21.7 (20.4, 22.9)	0.2 (−2.5, 2.9)	24.4 (22.9, 25.9)	0.2 (−2.8, 3.5)
		Telmisartan	21.9 (19.5, 24.2)		24.7 (21.9, 27.4)	
	Triple	Ramipril	20.1 (18.8, 21.3)	0.2 (−2.3, 2.8)	23.6 (22.1, 25.2)	0.1 (−2.7, 3.5)
		Telmisartan	20.2 (18.0, 22.5)		23.8 (21.2, 26.7)	
5 years	Baseline	Ramipril	29.4 (27.8, 30.9)	0.2 (−2.8, 3.7)	32.6 (30.6, 34.3)	0.4 (−3.2, 4.3)
		Telmisartan	29.7 (26.9, 32.7)		32.9 (29.8, 36.5)	
	Double	Ramipril	25.7 (24.3, 27.2)	0.3 (−2.8, 3.3)	30.7 (28.7, 32.7)	0.2 (−3.6, 4.2)
		Telmisartan	26.0 (23.3, 28.7)		31.0 (27.6, 34.8)	
	Triple	Ramipril	23.0 (21.7, 24.4)	0.2 (−2.3, 3.1)	29.0 (27.1, 31.1)	0.3 (−3.5, 4.7)
		Telmisartan	23.2 (20.7, 25.9)		29.4 (26.1, 33.3)	

Table 50. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the plasmode-simulated cohorts at 1, 3, and 5 years by mortality rate manipulation, according to age strata

Risk Time	Mortality Rate	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
Age 55−64				
1 year	Baseline	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	Double	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.1)	
	Triple	Ramipril	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.1)	
3 years	Baseline	Ramipril	0.1 (0.1, 0.1)	0.0 (−0.1, 0.1)
		Telmisartan	0.1 (0.0, 0.2)	
	Double	Ramipril	0.1 (0.1, 0.2)	0.0 (−0.1, 0.1)
		Telmisartan	0.2 (0.1, 0.3)	
	Triple	Ramipril	0.2 (0.2, 0.3)	0.0 (−0.1, 0.2)
		Telmisartan	0.2 (0.1, 0.4)	
5 years	Baseline	Ramipril	0.2 (0.1, 0.3)	0.0 (−0.1, 0.2)
		Telmisartan	0.2 (0.1, 0.4)	
	Double	Ramipril	0.4 (0.3, 0.5)	0.0 (−0.2, 0.3)
		Telmisartan	0.4 (0.2, 0.6)	
	Triple	Ramipril	0.5 (0.4, 0.7)	0.0 (−0.3, 0.4)
		Telmisartan	0.5 (0.3, 0.9)	
Age 65−74				
1 year	Baseline	Ramipril	0.1 (0.0, 0.1)	0.0 (−0.1, 0.1)
		Telmisartan	0.1 (0.0, 0.1)	
	Double	Ramipril	0.1 (0.1, 0.2)	0.0 (−0.1, 0.1)
		Telmisartan	0.1 (0.1, 0.2)	
	Triple	Ramipril	0.2 (0.1, 0.2)	0.0 (−0.1, 0.1)
		Telmisartan	0.2 (0.1, 0.2)	
3 years	Baseline	Ramipril	0.4 (0.3, 0.5)	0.0 (−0.2, 0.2)
		Telmisartan	0.4 (0.3, 0.6)	
	Double	Ramipril	0.7 (0.6, 0.8)	0.0 (−0.2, 0.3)
		Telmisartan	0.7 (0.5, 1.0)	
	Triple	Ramipril	1.0 (0.8, 1.2)	0.0 (−0.3, 0.4)
		Telmisartan	1.0 (0.7, 1.3)	
5 years	Baseline	Ramipril	0.9 (0.7, 1.1)	0.0 (−0.3, 0.4)
		Telmisartan	0.8 (0.6, 1.3)	
	Double	Ramipril	1.5 (1.3, 1.8)	0.0 (−0.5, 0.6)
		Telmisartan	1.5 (1.1, 2.1)	
	Triple	Ramipril	2.0 (1.7, 2.4)	0.0 (−0.7, 0.8)
		Telmisartan	2.0 (1.5, 2.7)	
Age 75+				
1 year	Baseline	Ramipril	0.3 (0.2, 0.4)	0.0 (−0.2, 0.4)
		Telmisartan	0.3 (0.2, 0.6)	
	Double	Ramipril	0.5 (0.4, 0.6)	0.0 (−0.2, 0.4)
		Telmisartan	0.5 (0.3, 0.9)	
	Triple	Ramipril	0.7 (0.6, 0.8)	0.0 (−0.2, 0.4)
		Telmisartan	0.7 (0.5, 1.1)	
3 years	Baseline	Ramipril	1.6 (1.4, 1.8)	0.0 (−0.4, 0.6)
		Telmisartan	1.6 (1.2, 2.2)	
	Double	Ramipril	2.7 (2.4, 3.1)	0.1 (−0.7, 0.9)
		Telmisartan	2.8 (2.1, 3.6)	
	Triple	Ramipril	3.5 (3.1, 4.1)	0.0 (−1.0, 1.2)
		Telmisartan	3.6 (2.8, 4.7)	
5 years	Baseline	Ramipril	3.2 (2.7, 3.7)	0.0 (−0.9, 1.3)
		Telmisartan	3.2 (2.4, 4.3)	
	Double	Ramipril	5.0 (4.3, 5.8)	0.1 (−1.4, 1.9)
		Telmisartan	5.0 (3.9, 6.7)	
	Triple	Ramipril	6.0 (5.3, 7.1)	0.1 (−1.7, 2.4)
		Telmisartan	6.1 (4.6, 8.2)	

Exploratory Analysis

The results of the exploratory analysis, in which we manipulated the associations between an exogenous variable X with both disenrollment and death in fully synthetically simulated cohorts, are shown in **Table 51**–**Table 52** and **Figure 42**–**Figure 44**. The baseline scenario, in which variable X has a null association with both disenrollment and death, serves as a comparison for the alternative scenarios (and is identical to the baseline scenario for the mortality manipulation; **Figure 42A**). Among ramipril users, the average 5-year sub-distribution and cause-specific cumulative risks per 100 under the baseline scenario were 23.9 (23.5, 24.3) and 26.0 (25.5, 26.4), respectively (difference = 2.1). In the next scenario, for which X had a strong protective association with both death and disenrollment (HR = 0.2 for death; HR = 0.2 for disenrollment), the average differences between the cause-specific and sub-distribution models across follow-up were less than that of the baseline scenario (**Figure 42B**). The average difference in 5-year cumulative risks per 100 under this scenario for ramipril users was 1.2. Alternatively, when predictor X had a strong harmful association with both death and disenrollment (HR = 5.0 for death; HR = 5.0 for disenrollment), the average differences in cumulative risks were increased compared to the baseline scenario (5-year difference in cumulative risks per 100 among ramipril users = 2.0; **Figure 42C**). Finally, the average differences in cumulative risks comparing the cause-specific and sub-distribution models were greatest when predictor X had strong associations of opposite directionality with death and disenrollment (5-year difference in cumulative risks per 100 among ramipril users = 5.0; **Figure 42C**). Across all four scenarios at 5 years, the largest average difference in risk differences per 100 from the cause-specific versus sub-distribution models was an absolute value of 0.7 (**Table 52** and **Figure 44**).

Figure 42. Average cumulative risk estimates of the composite outcome from the sub-distribution and cause-specific models in the fully simulated cohorts under manipulations of the associations between variable X with disenrollment and death

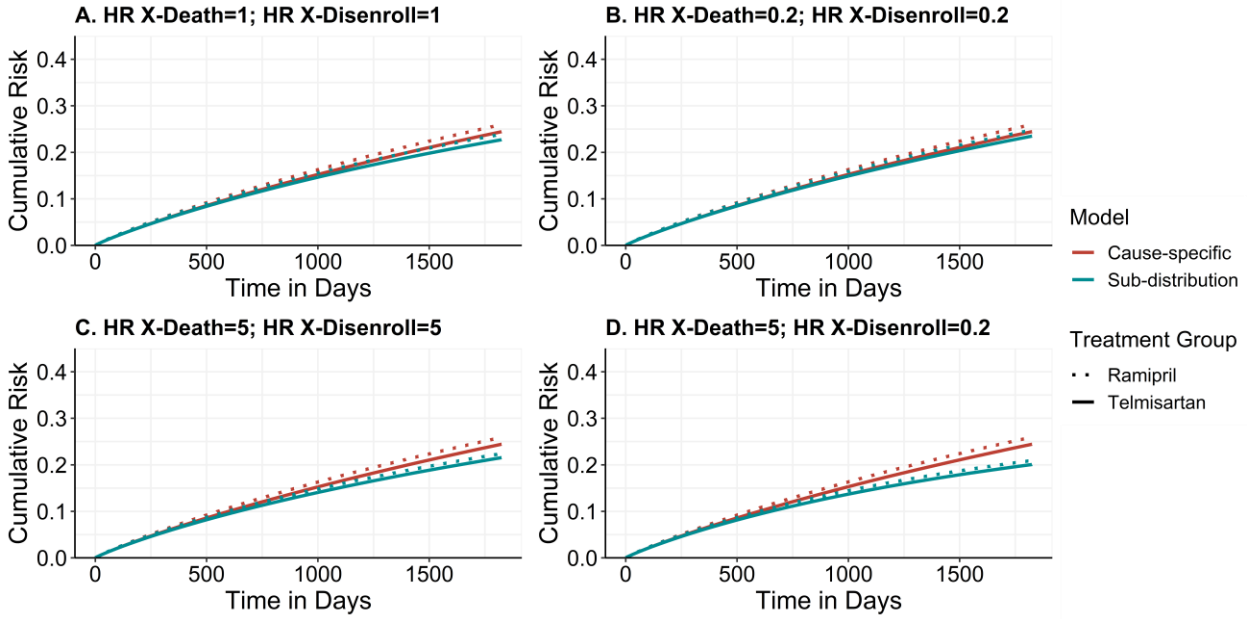


Table 51. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts under manipulations of the associations between variable X with disenrollment and death

Predictor Relationship	Treatment Group	Sub-Distribution		Cause-Specific	
		Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
1 Year					
HR X-Death=1 HR X-Disenroll=1	Ramipril	6.9 (6.7, 7.1)	−0.5 (−0.8, −0.1)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.4 (6.1, 6.8)		6.5 (6.2, 6.9)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	6.9 (6.8, 7.1)	−0.5 (−0.8, −0.1)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.5 (6.2, 6.8)		6.5 (6.2, 6.9)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	6.8 (6.6, 7.0)	−0.4 (−0.9, 0.0)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.3 (6.0, 6.7)		6.5 (6.2, 6.9)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	6.7 (6.6, 6.9)	−0.4 (−0.8, 0.0)	7.0 (6.8, 7.2)	−0.5 (−0.9, −0.1)
	Telmisartan	6.3 (6.0, 6.6)		6.6 (6.2, 6.9)	
3 Years					
HR X-Death=1 HR X-Disenroll=1	Ramipril	16.7 (16.3, 17.0)	−1.0 (−1.6, −0.3)	17.5 (17.2, 17.8)	−1.1 (−1.8, −0.4)
	Telmisartan	15.7 (15.2, 16.3)		16.4 (15.8, 17.0)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	17.0 (16.7, 17.3)	−1.0 (−1.6, −0.4)	17.5 (17.2, 17.8)	−1.1 (−1.7, −0.5)
	Telmisartan	16.0 (15.5, 16.5)		16.4 (15.9, 16.9)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	15.8 (15.5, 16.2)	−0.8 (−1.6, 0.0)	17.5 (17.1, 17.9)	−1.1 (−2.0, −0.2)
	Telmisartan	15.0 (14.4, 15.7)		16.4 (15.7, 17.1)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	15.4 (15.1, 15.6)	−0.8 (−1.4, −0.2)	17.6 (17.2, 17.9)	−1.1 (−1.8, −0.4)
	Telmisartan	14.6 (14.1, 15.1)		16.5 (15.9, 17.0)	
5 Years					
HR X-Death=1 HR X-Disenroll=1	Ramipril	23.9 (23.5, 24.3)	−1.2 (−2.0, −0.3)	26.0 (25.5, 26.4)	−1.5 (−2.4, −0.6)
	Telmisartan	22.7 (22.0, 23.4)		24.4 (23.7, 25.2)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	24.8 (24.5, 25.2)	−1.3 (−2.0, −0.6)	26.0 (25.6, 26.3)	−1.5 (−2.3, −0.8)
	Telmisartan	23.5 (22.9, 24.1)		24.5 (23.8, 25.1)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	22.4 (21.9, 22.9)	−0.9 (−2.0, 0.2)	25.9 (25.3, 26.5)	−1.5 (−2.7, −0.2)
	Telmisartan	21.5 (20.6, 22.5)		24.4 (23.4, 25.5)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	20.9 (20.6, 21.3)	−0.9 (−1.6, −0.2)	26.0 (25.5, 26.4)	−1.5 (−2.4, −0.7)
	Telmisartan	20.1 (19.5, 20.7)		24.4 (23.7, 25.2)	

Table 52. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the fully synthetically simulated cohorts at 1, 3, and 5 years under manipulations of the associations between variable X with disenrollment and death

Predictor Relationship	Treatment Group	Difference in Cumulative Risks / 100 (95% CI)	Difference in Risk Differences / 100 (95% CI)
1 Year			
HR X-Death=1 HR X-Disenroll=1	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.1 (0.1, 0.1)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
	Telmisartan	0.1 (0.0, 0.1)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	0.3 (0.3, 0.3)	−0.1 (−0.1, 0.0)
	Telmisartan	0.2 (0.2, 0.2)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	0.3 (0.3, 0.3)	−0.1 (−0.1, 0.0)
	Telmisartan	0.2 (0.2, 0.3)	
3 Years			
HR X-Death=1 HR X-Disenroll=1	Ramipril	0.9 (0.8, 0.9)	−0.2 (−0.2, −0.1)
	Telmisartan	0.7 (0.6, 0.8)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.5 (0.5, 0.5)	−0.1 (−0.1, −0.1)
	Telmisartan	0.4 (0.4, 0.4)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	1.7 (1.6, 1.8)	−0.3 (−0.5, −0.2)
	Telmisartan	1.4 (1.3, 1.5)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	2.2 (2.1, 2.3)	−0.3 (−0.5, −0.2)
	Telmisartan	1.9 (1.8, 2.0)	
5 Years			
HR X-Death=1 HR X-Disenroll=1	Ramipril	2.1 (2.0, 2.2)	−0.3 (−0.5, −0.2)
	Telmisartan	1.7 (1.6, 1.9)	
HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	1.2 (1.1, 1.2)	−0.2 (−0.3, −0.1)
	Telmisartan	1.0 (0.9, 1.0)	
HR X-Death=5 HR X-Disenroll=5	Ramipril	3.5 (3.3, 3.6)	−0.6 (−0.9, −0.4)
	Telmisartan	2.9 (2.7, 3.1)	
HR X-Death=5 HR X-Disenroll=0.2	Ramipril	5.0 (4.9, 5.2)	−0.7 (−1.0, −0.4)
	Telmisartan	4.4 (4.1, 4.6)	

Figure 43. Average difference in cumulative risk estimates per 100 of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the fully synthetically simulated cohorts under manipulations of the associations between variable X with disenrollment and death

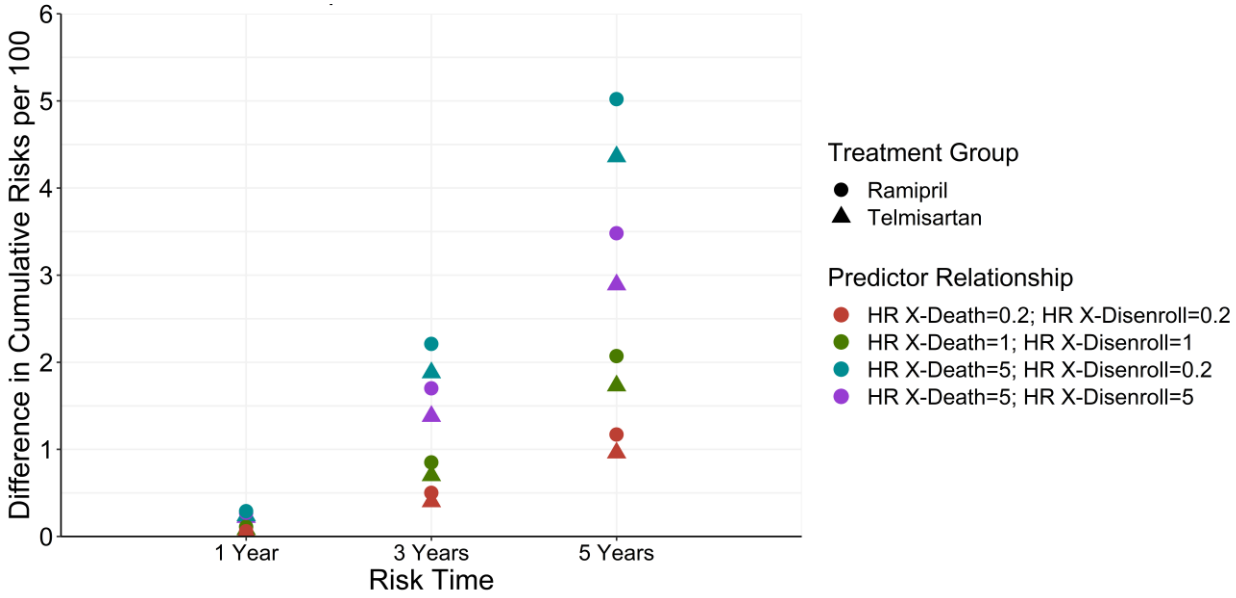
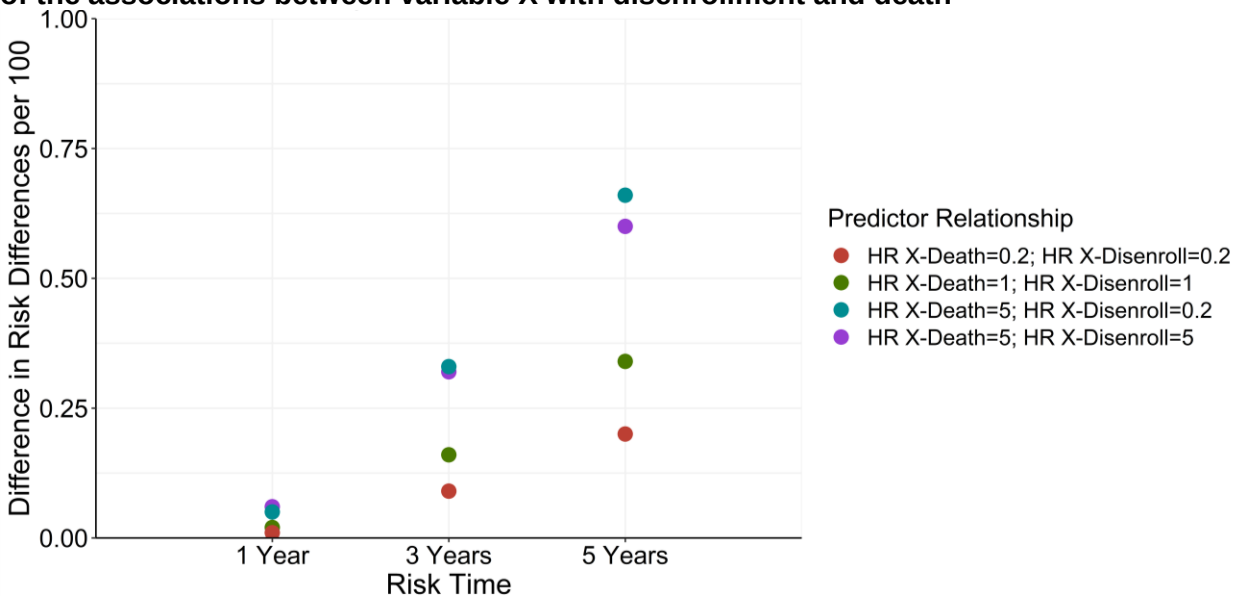


Figure 44. Average difference in risk difference estimates per 100 (telmisartan versus ramipril) of the composite outcome at 1, 3, and 5 years from the cause-specific versus sub-distribution models in the fully synthetically simulated cohorts under manipulations of the associations between variable X with disenrollment and death



The average age-stratified cumulative risk estimates from the cause-specific and sub-distribution models under manipulations of the predictors and death and disenrollment are displayed in **Table 53–Table 54** and **Figure 45**. In the youngest age strata, manipulating the relationships of variable X with death and disenrollment did not result in differences between the cause-specific and sub-distribution risk estimates, likely due to the low mortality rate (**Figure 45A–D**). The average difference in cumulative risks among the 65–74 age group was minor in the baseline scenario and first two manipulations, but more pronounced in the scenario in which X had strong relationships of opposite directionality with death and disenrollment, although the differences remained minor (**Figure 45E–H**). Finally, in the oldest age group, more pronounced differences were observed across the scenarios (**Figure 45I–L**). Among ramipril users age 75+, the average 5-year cause-specific and sub-distribution risks per 100, respectively, were 43.5 (42.5, 44.6) and 37.3 (36.4, 38.2) under the baseline scenario (difference = 6.2) and were 43.6 (42.4, 44.7) and 29.5 (28.7, 30.2) under the scenario in which X had strong associations of opposite directionality with death and disenrollment (difference = 14.1).

Figure 45. Average cumulative risk estimates of the composite outcome sub-distribution and cause-specific models in the fully synthetically simulated cohorts under manipulations of the associations between variable X with disenrollment and death and according to age strata

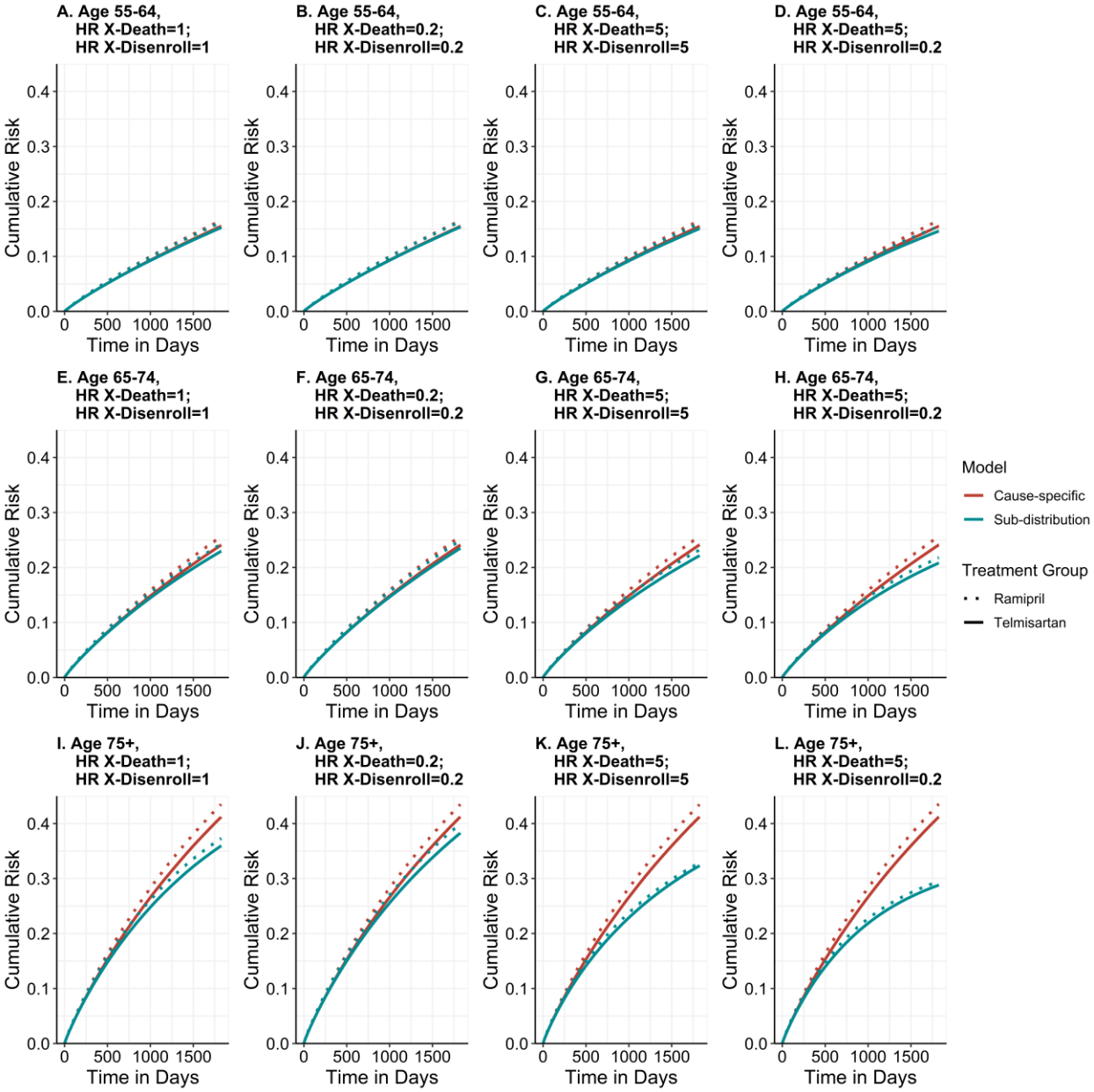


Table 53. Average cumulative risks and risk differences per 100 of composite outcome at 1, 3, and 5 years from the sub-distribution and cause-specific models in the fully synthetically simulated cohorts under manipulations of the associations between variable X with disenrollment and death and according to age strata

Risk Time	Predictor Relationship	Treatment Group	Sub-Distribution		Cause-Specific	
			Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
Age 55−64						
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	4.2 (3.9, 4.4) 3.9 (3.4, 4.3)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4) 3.9 (3.4, 4.3)	−0.3 (−0.8, 0.2)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	4.2 (3.9, 4.4) 3.9 (3.4, 4.3)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4) 3.9 (3.5, 4.3)	−0.3 (−0.8, 0.2)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	4.1 (3.9, 4.4) 3.9 (3.3, 4.4)	−0.3 (−0.9, 0.3)	4.2 (3.9, 4.4) 3.9 (3.4, 4.4)	−0.3 (−0.9, 0.3)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	4.1 (3.9, 4.3) 3.8 (3.4, 4.3)	−0.3 (−0.8, 0.2)	4.2 (3.9, 4.4) 3.9 (3.4, 4.3)	−0.3 (−0.8, 0.2)
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	10.7 (10.2, 11.1) 10.0 (9.2, 10.8)	−0.7 (−1.7, 0.3)	10.8 (10.3, 11.2) 10.1 (9.2, 10.9)	−0.7 (−1.7, 0.3)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	10.7 (10.4, 11.1) 10.0 (9.3, 10.7)	−0.7 (−1.5, 0.1)	10.8 (10.4, 11.2) 10.1 (9.4, 10.8)	−0.7 (−1.5, 0.1)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	10.6 (10.0, 11.1) 9.9 (8.8, 11.0)	−0.7 (−1.9, 0.6)	10.8 (10.2, 11.3) 10.1 (9.0, 11.2)	−0.7 (−2.0, 0.6)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	10.4 (10.1, 10.8) 9.8 (9.1, 10.5)	−0.6 (−1.4, 0.2)	10.8 (10.4, 11.2) 10.1 (9.3, 10.8)	−0.7 (−1.5, 0.1)
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	16.2 (15.6, 16.8) 15.2 (14.0, 16.5)	−1.0 (−2.4, 0.4)	16.5 (15.9, 17.2) 15.5 (14.3, 16.8)	−1.0 (−2.4, 0.4)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	16.4 (15.9, 16.8) 15.4 (14.4, 16.3)	−1.0 (−2.1, 0.0)	16.5 (16.1, 17.0) 15.5 (14.5, 16.4)	−1.0 (−2.1, 0.0)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	16.0 (15.2, 16.8) 15.1 (13.4, 16.8)	−0.9 (−2.8, 1.0)	16.5 (15.7, 17.4) 15.5 (13.7, 17.3)	−1.1 (−3.0, 0.9)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	15.5 (15.0, 16.0) 14.6 (13.7, 15.6)	−0.9 (−1.9, 0.2)	16.5 (16.0, 17.1) 15.5 (14.5, 16.5)	−1.0 (−2.2, 0.1)
Age 65−74						
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	6.7 (6.4, 7.0) 6.2 (5.7, 6.8)	−0.5 (−1.1, 0.2)	6.7 (6.4, 7.1) 6.3 (5.7, 6.8)	−0.5 (−1.1, 0.2)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	6.7 (6.4, 7.0) 6.2 (5.7, 6.8)	−0.5 (−1.1, 0.1)	6.7 (6.4, 7.1) 6.3 (5.8, 6.8)	−0.5 (−1.1, 0.1)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	6.6 (6.3, 6.9) 6.2 (5.6, 6.7)	−0.5 (−1.1, 0.2)	6.7 (6.4, 7.1) 6.3 (5.7, 6.9)	−0.5 (−1.1, 0.2)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	6.6 (6.3, 6.9) 6.2 (5.6, 6.7)	−0.4 (−1.0, 0.2)	6.7 (6.4, 7.1) 6.3 (5.8, 6.8)	−0.5 (−1.1, 0.2)
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	16.6 (16.0, 17.1) 15.6 (14.6, 16.5)	−1.0 (−2.1, 0.1)	17.1 (16.5, 17.6) 16.0 (15.0, 16.9)	−1.1 (−2.2, 0.0)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	16.8 (16.3, 17.3) 15.8 (14.9, 16.6)	−1.1 (−2.0, −0.1)	17.1 (16.6, 17.6) 16.0 (15.2, 16.8)	−1.1 (−2.1, −0.1)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	16.0 (15.4, 16.6) 15.1 (14.1, 16.2)	−0.9 (−2.1, 0.4)	17.1 (16.4, 17.8) 16.0 (14.9, 17.1)	−1.1 (−2.4, 0.2)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	15.6 (15.1, 16.1) 14.8 (13.9, 15.6)	−0.8 (−1.8, 0.1)	17.1 (16.6, 17.6) 16.0 (15.1, 16.9)	−1.1 (−2.2, 0.0)
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	24.3 (23.6, 24.9) 23.0 (21.7, 24.2)	−1.3 (−2.7, 0.1)	25.6 (24.9, 26.4) 24.1 (22.8, 25.4)	−1.6 (−3.0, −0.1)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	24.9 (24.3, 25.6) 23.5 (22.5, 24.5)	−1.5 (−2.6, −0.3)	25.7 (25.1, 26.3) 24.1 (23.1, 25.1)	−1.6 (−2.8, −0.4)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	23.2 (22.4, 24.1) 22.2 (20.7, 23.6)	−1.1 (−2.7, 0.6)	25.7 (24.7, 26.6) 24.1 (22.5, 25.7)	−1.6 (−3.4, 0.3)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	21.8 (21.2, 22.3) 20.8 (19.8, 21.8)	−1.0 (−2.1, 0.2)	25.7 (25.0, 26.3) 24.1 (22.9, 25.3)	−1.6 (−2.9, −0.2)
Age 75+						
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	12.3 (11.8, 12.8) 11.5 (10.7, 12.3)	−0.8 (−1.7, 0.2)	12.6 (12.0, 13.1) 11.7 (10.9, 12.6)	−0.8 (−1.8, 0.1)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	12.4 (11.9, 12.9) 11.6 (10.8, 12.4)	−0.8 (−1.8, 0.2)	12.6 (12.0, 13.1) 11.7 (10.9, 12.6)	−0.8 (−1.8, 0.2)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	11.8 (11.2, 12.3) 11.1 (10.2, 12.0)	−0.7 (−1.7, 0.4)	12.6 (12.0, 13.1) 11.7 (10.8, 12.7)	−0.8 (−1.9, 0.3)
	HR X-Death=5	Ramipril	11.7 (11.2, 12.2)	−0.7 (−1.6, 0.3)	12.6 (12.0, 13.1)	−0.8 (−1.8, 0.2)

Risk Time	Predictor Relationship	Treatment Group	Sub-Distribution		Cause-Specific	
			Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)	Cumulative Risk / 100 (95% CI)	Risk Difference / 100 (95% CI)
	HR X-Disenroll=0.2	Telmisartan	11.0 (10.2, 11.8)		11.8 (10.9, 12.6)	
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril	27.7 (27.0, 28.5)	−1.4 (−2.8, 0.1)	30.3 (29.5, 31.1)	−1.8 (−3.4, −0.2)
		Telmisartan	26.4 (25.1, 27.6)		28.5 (27.1, 29.8)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	28.8 (28.0, 29.5)	−1.5 (−2.9, −0.1)	30.3 (29.5, 31.1)	−1.8 (−3.2, −0.3)
		Telmisartan	27.3 (26.1, 28.5)		28.5 (27.3, 29.8)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	25.1 (24.2, 25.9)	−0.9 (−2.6, 0.9)	30.3 (29.2, 31.3)	−1.8 (−3.9, 0.3)
		Telmisartan	24.2 (22.8, 25.7)		28.5 (26.7, 30.3)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	23.8 (23.1, 24.5)	−0.8 (−2.2, 0.5)	30.3 (29.4, 31.2)	−1.8 (−3.4, −0.1)
		Telmisartan	23.0 (21.9, 24.1)		28.5 (27.2, 29.9)	
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril	37.3 (36.4, 38.2)	−1.3 (−3.1, 0.4)	43.5 (42.5, 44.6)	−2.3 (−4.4, −0.2)
		Telmisartan	36.0 (34.5, 37.5)		41.2 (39.4, 43.0)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	40.0 (39.1, 40.8)	−1.7 (−3.3, 0.0)	43.5 (42.6, 44.4)	−2.3 (−4.0, −0.5)
		Telmisartan	38.3 (36.9, 39.7)		41.2 (39.8, 42.7)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	32.9 (31.8, 33.9)	−0.5 (−2.7, 1.6)	43.5 (42.1, 44.9)	−2.3 (−5.1, 0.6)
		Telmisartan	32.3 (30.5, 34.2)		41.2 (38.8, 43.7)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	29.5 (28.7, 30.2)	−0.7 (−2.1, 0.8)	43.6 (42.4, 44.7)	−2.3 (−4.6, −0.1)
		Telmisartan	28.8 (27.6, 30.0)		41.2 (39.4, 43.1)	

Table 54. Average difference in cumulative risks per 100 and difference in risk differences per 100 (telmisartan versus ramipril) comparing cause-specific and sub-distribution risk of composite outcome in the fully synthetically simulated cohorts at 1, 3, and 5 years under manipulations of the associations between variable X with disenrollment and death and according to age strata

Risk Time	Predictor Relationship	Treatment Group	Difference in Cumulative Risks / 100	Difference in Risk Differences / 100
Age 55−64				
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril	0.1 (0.1, 0.1)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.1)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
		Telmisartan	0.1 (0.0, 0.1)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	0.2 (0.2, 0.3)	−0.1 (−0.1, 0.0)
		Telmisartan	0.2 (0.1, 0.2)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	0.4 (0.3, 0.4)	−0.1 (−0.1, 0.0)
		Telmisartan	0.3 (0.3, 0.4)	
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril	0.3 (0.3, 0.4)	−0.1 (−0.1, 0.0)
		Telmisartan	0.3 (0.2, 0.3)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.2 (0.2, 0.2)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.2)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	0.5 (0.5, 0.6)	−0.1 (−0.2, 0.0)
		Telmisartan	0.4 (0.3, 0.5)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	1.1 (1.0, 1.1)	−0.2 (−0.3, 0.0)
		Telmisartan	0.9 (0.8, 1.0)	
Age 65−74				
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.1)	
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
		Telmisartan	0.0 (0.0, 0.0)	
	HR X-Death=5 HR X-Disenroll=5	Ramipril	0.1 (0.1, 0.2)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.1)	
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril	0.2 (0.2, 0.2)	0.0 (−0.1, 0.0)
		Telmisartan	0.1 (0.1, 0.2)	
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril	0.5 (0.5, 0.5)	−0.1 (−0.2, 0.0)
		Telmisartan	0.4 (0.4, 0.5)	

	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	0.3 (0.3, 0.3) 0.2 (0.2, 0.3)	−0.1 (−0.1, 0.0)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	1.1 (1.0, 1.2) 0.9 (0.8, 1.0)	−0.2 (−0.4, −0.1)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	1.5 (1.4, 1.6) 1.2 (1.1, 1.4)	−0.3 (−0.4, −0.1)
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	1.4 (1.3, 1.5) 1.1 (1.0, 1.3)	−0.2 (−0.4, −0.1)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	0.8 (0.7, 0.8) 0.6 (0.5, 0.7)	−0.1 (−0.2, −0.1)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	2.5 (2.3, 2.6) 2.0 (1.7, 2.2)	−0.5 (−0.8, −0.2)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	3.9 (3.7, 4.1) 3.3 (3.0, 3.6)	−0.6 (−0.9, −0.3)
Age 75+				
1 year	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	0.3 (0.3, 0.3) 0.3 (0.2, 0.3)	−0.1 (−0.1, 0.0)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	0.2 (0.2, 0.2) 0.2 (0.1, 0.2)	0.0 (−0.1, 0.0)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	0.8 (0.7, 0.9) 0.7 (0.6, 0.7)	−0.2 (−0.3, 0.0)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	0.9 (0.8, 0.9) 0.7 (0.6, 0.8)	−0.2 (−0.3, −0.1)
3 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	2.6 (2.4, 2.7) 2.1 (1.9, 2.3)	−0.4 (−0.7, −0.2)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	1.5 (1.4, 1.6) 1.2 (1.1, 1.4)	−0.3 (−0.4, −0.1)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	5.2 (4.9, 5.5) 4.3 (3.8, 4.7)	−0.9 (−1.5, −0.4)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	6.5 (6.2, 6.8) 5.6 (5.1, 6.0)	−0.9 (−1.5, −0.4)
5 years	HR X-Death=1 HR X-Disenroll=1	Ramipril Telmisartan	6.2 (5.9, 6.5) 5.3 (4.8, 5.7)	−1.0 (−1.6, −0.4)
	HR X-Death=0.2 HR X-Disenroll=0.2	Ramipril Telmisartan	3.5 (3.4, 3.7) 3.0 (2.7, 3.2)	−0.6 (−0.9, −0.2)
	HR X-Death=5 HR X-Disenroll=5	Ramipril Telmisartan	10.6 (10.0, 11.2) 8.9 (8.0, 9.8)	−1.7 (−2.8, −0.7)
	HR X-Death=5 HR X-Disenroll=0.2	Ramipril Telmisartan	14.1 (13.4, 14.7) 12.4 (11.4, 13.4)	−1.7 (−2.8, −0.5)

Discussion

Overall, specification of death as a censoring event, as compared to a competing event, was observed to have a greater impact on cumulative risk estimation in later years of follow-up. In the main analyses using the overall Optum cohort, cumulative risk curves for both the telmisartan and ramipril groups overlapped for the first three years of follow-up, meaning that the cause-specific risk estimator was approximating the sub-distribution model. However, the cumulative risk curves diverged slightly in later years of follow-up, such that at year 5 the difference in the cause-specific model was a difference of about 1% in risk for both treatment groups. This is as expected given that, by definition, the cumulative risk of mortality increases

across follow-up; about 6% of the overall cohort had died at year 5 compared to less than 1% at year 1. Therefore, at year 5, compared to year 1, there is expected to be a greater upweighting of outcome events in the cause-specific risk estimator given the greater total proportion of censoring due to death that has occurred by that time.[220]

Stratification on patient age group further demonstrated the relationship between difference in cumulative risks due to specification of death as a censoring event, as compared to as a competing event. In general, the cumulative risk curves for both treatment groups were observed to be completely overlapping for the entirety of the follow-up period in the youngest age group (where the mortality risks and rates were notably lower than those of the overall cohort), indicating there to be no difference in the cause-specific risk estimator. The cumulative risk curves were observed to diverge slightly for the 65–74 age group (for which the mortality risk and rates, although higher than that of the youngest age group, were still lower than that of the overall cohort), and even more so for the 75+ age group, especially in later follow-up where the risk of mortality was the highest. The largest difference in cumulative risks observed was in the 75+ age group at 5 years, and was a difference in about 3–4% in the cumulative risk of the outcome for both treatment groups.

The simulations allowed us to examine the influence on resulting cumulative risk estimates of mortality rate specifically, while maintaining outcome and censoring rates, which may not have been the case in the age-stratified Optum analyses. Additionally, the simulations allowed us to expand upon the age-stratified results of the Optum cohort, which were based on a limited range of mortality risks (<1% in the youngest age group at year 1 to 14% in the oldest age group at year 5), by introducing a greater range of mortality risks (up to nearly 40% risk of mortality at year 5 under tripling of the mortality rate). Simulation results, from both the fully synthetically simulated and plasmode-simulated cohorts, corroborated the previously observed patterns by demonstrating differences in cumulative risks due to censoring on death to increase

with increasing mortality rate, independently of outcome and censoring rates.

In exploratory analyses, in which we manipulated the relationships that an exogenous variable had with death and with disenrollment, the largest difference in cumulative risks was observed when the variable was strongly, directly associated with death yet strongly, inversely associated with disenrollment. Characteristics in claims that may meet this variable definition include older age, limited life expectancy, and markers of frailty (e.g., supplemental oxygen, mobility aids), which are expected to correspond to patients at an increased risk of death yet a decreased likelihood of disenrollment, likely given their nearness to end of life and dependence on healthcare.[215] The presence of this variable likely resulted in increased difference in cumulative risks via its relative impacts on the mortality and disenrollment rates, which would have resulted in a greater proportion of overall censoring events in the cause-specific model being due to death rather than disenrollment. Notably, in the overall Optum cohort, including mortality as a censoring event meant that about 10% of loss to follow-up was truly a competing event; this proportion ranged from about 2% in the youngest age group to nearly 30% in the oldest age group. In the exploratory simulations, when the associations between the predictor variable with death and disenrollment were of shared directionality, manipulating the associations from null to strongly protective to strongly harmful did not alter the proportion of loss to follow-up in cause-specific models that was due to death (about 6% across these three scenarios for the overall simulated cohorts). However, when the variable was strongly, directly associated with death yet strongly, inversely associated with disenrollment, this proportion increased to about 25% (and was greater than 50% in the oldest age group). This observation suggests the difference in cumulative risks due to censoring on a competing event to be driven not only by the rate of the competing event, but also by this rate relative to the rate of other censoring events. Future work may consider how the ratio of competing events to censoring events may impact differences in cumulative risks and how quantitative bias analyses using estimations of this ratio may be used

to adjust for such differences when true death information is incomplete or unavailable.[229]

Across the Optum overall and age-stratified analyses, the difference in the cause-specific versus sub-distribution models was similar for the telmisartan and ramipril groups, such that the resulting difference in this difference was quite small; the difference in the risk differences did not exceed 1.0%. We suspect this observation is due to the similar mortality and censoring rates of the two treatment groups. Future work may further examine how differentially varying the mortality rates of the treatment groups (i.e., varying the association between exposure and the competing event) to make the mortality and censoring rates dissimilar may impact the difference in the cause-specific risk differences. This type of treatment-specific competing event rate manipulation has not previously been explored in a claims-based setting in an age-stratified manner, but would be meaningful to inform database choices specifically for comparative safety and effectiveness research.[224]

Few studies have explored the impact of ignoring competing events under simulated scenarios, and, to our knowledge, none have demonstrated the impact in relation to patient cohort age strata and mortality rate.[224, 225, 229] In a cohort of older adults with a prior hip fracture, Berry et al. examined the cumulative risk and hazard ratio of second hip fracture associated with age (at 1, 3, 5, and 10 years), varying the mortality risk between 10 and 85%. It was observed that as the risk of mortality increased, the magnitude of difference between models that did, versus did not, account for the competing events increased accordingly.[225] An increase in the difference between the sub-distribution and cause-specific risk models over follow-up time was also noted, similar to our analyses.[225]

This analysis has several limitations. First, as this study is based on the analysis of automated medical and prescription claims data, our analysis is subject to the inherent limitations of using claims data for research purposes. Particularly, the diagnoses and prescription medications reported in claims data may not be an accurate reflection of an individual’s health and

medication usage. For the severe conditions in this analysis, we do expect the associated diagnoses, procedures, and medication usage to be accurately recorded. Nevertheless, given that the primary goal of this analysis was not to estimate a treatment effect, but rather to demonstrate a methodological issue, we are not concerned about the impact of systematic issues in claims data coding on our ability to demonstrate differences in sub-distribution versus cause-specific models.

It is also important to consider that our analysis assumed the sub-distribution model to be the gold standard, meaning that all death events were assumed to be completely captured and specified as competing events. In reality, it is possible that death events may have been undercounted, in which case some missed death events would have been indirectly treated as censoring events. In November 2011, the Social Security Administration Death Master File, which supplements Optum's claims-based death information, implemented changes to suppress death records received from states.[253] This change resulted in the removal of 4.2 million historic death records, and the loss of about 1 million annual deaths.[254] This would impact our estimates of the gold standard parameters, such that the sub-distribution risk estimators may not have been accurately accounting for all death events as assumed. Instead, some of the death events that were not reported from the states were likely indirectly treated as disenrollment censoring events. As a result, our sub-distribution cumulative risks would be overestimated due to the inappropriate censoring of true death events, especially for the oldest age group where the mortality rate is the highest. This would result in our estimates of the difference in the cause-specific, compared to sub-distribution, risks being conservative estimates of the difference.

Finally, it is worth noting that our analysis demonstrated an extreme scenario in which all death events were inappropriately counted as censoring events, whereas in reality, a database with incomplete death information may actually allow for a partial account of the competing event of death. If a proportion, but not all, of the death events were to be counted as competing events,

the difference in the cause-specific, compared to the sub-distribution, risk estimator would be maximized at what was observed under our extreme scenario of censoring on all deaths. This may be reassuring, especially for cohorts with mortality rates similar to or less than those of our younger age strata, given that the difference observed in our analyses for these groups were already low to negligible. If researchers remain unsure about the impact of incomplete, yet not entirely missing, death information, sensitivity analyses are possible in which a varying proportion of censoring events may be assumed to be unobserved deaths. Correction factors and machine learning techniques have been proposed in the literature as methods to address incomplete death information.[255, 256]

Overall, this analysis demonstrates how the effect estimates derived from real-world data may be impacted by the inability to distinguish death from other reasons for loss to follow-up, such as health plan disenrollment. Our claims-based cohort analysis and simulations allowed us to compare estimates obtained when death was specified as a competing event, as would be possible in a death-information-linked data source, versus when death was specified as a censoring event, as would occur in other healthcare databases with missing or incomplete death information, under variations in population characteristics, consistent with different patient cohorts. These results encourage appropriate fit-for-purpose database choices, which has important implications for ensuring the delivery of reliable information to patients, providers, and healthcare practices. We recommend future researchers consider their patient cohort's underlying mortality rate when deciding whether a data source lacking complete death information is a viable option. As we observed the difference in risk differences across time for all age groups to be less than an absolute value of 1%, these considerations are particularly relevant for descriptive research questions aimed at summarizing disease occurrence, rather than for measures of association (assuming mortality and censoring rates to be similar between the treatment groups of interest). In general, if mortality rate is high or follow-up is long, a data

source with complete death information is preferable for cumulative risk estimation, given the substantial cumulative risk overestimation that would occur were all deaths to be censored. If mortality rate is low or follow-up time is short enough such that the risk of mortality remains low throughout the entirety of follow-up, a data source with incomplete death information may be used without worrying that the competing event of death will substantially influence event risk estimations. The choice of database should be made on a case-by-case basis depending on the research needs, taking into consideration where larger sample sizes may be available, depending on the patient population and treatment effect of interest, and what types of external data sources can be linked. If a data source lacking complete death information seems to provide advantages over one with complete death information, relative to the research needs, and the research team is confident that mortality risk is low across follow-up, then the data source with incomplete death information may be used without concern.

CHAPTER 5: SUMMARY OF RESULTS AND FUTURE RESEARCH

The overarching goal of this dissertation was to evaluate the validity of aspects of healthcare database research in the pharmaceutical industry and to assess how pharmacoepidemiologic methods can be applied to appropriately chosen real-world data sources to deliver valid real-world-based evidence regarding medication safety and effectiveness. Although premarketing efficacy trials are vital for informing whether a new drug product has the ability to treat the indicated condition, the variability of circumstances in the real world (e.g., physician prescribing and dosing choices, patient comorbidities and behavior, polypharmacy, etc.) necessitate evaluation of effectiveness of the drug in routine clinical practice. Understanding how data generated from the financing, insurance, and delivery of healthcare can be appropriately used to measure the real-world safety and effectiveness of drug products has implications for patients, physicians, practices, and regulatory agencies.

To address the overarching dissertation goal, we proposed the following aims. Aim 1 involved the creation and assessment of a mother–infant claims linkage and served to determine the suitability of this data source to produce valid, reproducible estimates of infant outcomes associated with *in utero* medication exposure. Aim 2 evaluated the comparative hematologic safety of multiple myeloma treatment regimens following two lines of therapy and served to demonstrate how pharmacoepidemiologic methods can be used to address comparative safety questions in the face of confounding bias due to complex, non-randomized prescribing patterns. Aim 3 used claims-based and plasmode-simulated study cohorts to demonstrate the impact on cumulative risk estimates of specifying death as a censoring event, rather than as a competing event, as would occur in databases with incomplete death information. This aim served to allow future researchers to predict the impact of incomplete death information based on patient population characteristics (particularly age and mortality rate). In this chapter, we review the major findings of each aim, followed by a discussion of potential future research directions.

Review of Major Findings

In Aim 1, we used the Duke-Margolis framework to assess whether a linked cohort of mothers and infants in the Japan Medical Data Center (JMDC) claims database is fit for purpose within the regulatory context of estimating infant outcomes associated with *in utero* exposure to marketed medications. The Duke-Margolis framework considers whether a database is fit for regulatory purpose based on relevancy and quality. To assess these considerations, we estimated the number of pregnancies that could be linked to an infant among females 12–55 years in the JMDC claims database between January 2005 and March 2022 using two different linkage approaches and examined descriptive characteristics. In terms of relevancy, we determined that critical data fields (maternal medication exposures, infant major congenital malformations, covariates) were available. A total of 385,295 valid mother–infant pairs were identified and about 41,000 congenital malformations were observed among these pairs. Comparison to publicly available data from Japan suggested that preterm births were under-recorded (3.6% versus 5.6%) in this population. Although overall congenital malformations were over-represented (10.8% versus 5.3%) in this population, the prevalence of specific malformation subcategories were consistent with the general population. Maternal characteristics appeared mostly consistent with the population of same-aged females in Japan. In terms of quality, our methods were expected to accurately identify the complete set of mothers and infants in the JMDC enrolled in a shared health insurance plan. Examination of values indicated for the relationship of the “mother” and “infant” to the insurance holder allowed for confirmation of assumed biologic mother–infant pairs. However, the completeness and accuracy of gestational age information was limited given the lack of live birth delivery codes for 60% of the cohort coupled with suppression of infant birth dates and inaccessibility of International Classification of Diseases codes with fifth level digits (where gestational week information would have been available) in the database. These results suggest that the JMDC

claims database may be well-suited for descriptive studies of pregnant people in Japan (e.g., comorbidities, medication usage), but more work is needed to identify a method to assign pregnancy onset and delivery dates so that *in utero* exposure windows can be defined more precisely as needed for many regulatory postapproval pregnancy safety studies.

In Aim 2, we sought to evaluate the risks of severe cytopenias in relapsed multiple myeloma patients who received sequential treatment with regimens containing immunomodulatory agents (IMiDs) versus IMiD-free regimens. The Flatiron Health database was used to identify a cohort of 5,573 patients at least 18 years of age who were diagnosed with multiple myeloma between January 2011 and December 2020 and subsequently received at least two lines of therapy (LOTs). Those for which both LOTs contained IMiDs were considered “sequentially exposed”; those for which neither contained IMiDs were “never exposed.” Inverse probability of treatment weighted cumulative risks up to 12 months were estimated for each exposure group and risk differences were calculated. Analyses were repeated stratified by recent cytopenia history, age, and cytogenetic risk. The 1-year risks of neutropenia and leukopenia were substantially higher among those exposed versus unexposed to IMiDs at LOT 2 and stratification on prior IMiD exposure revealed a trend in which, compared to those never exposed, those sequentially exposed had the highest 1-year risk, followed by those only recently exposed during LOT 2, then by those with only past exposure during LOT 1. This observation did not hold for severe cytopenias not related to white blood cells (anemia, lymphocytopenia, and thrombocytopenia). The associations between sequential, versus never, exposure with neutropenia and leukopenia were even stronger among those with a history of the given cytopenia, but were attenuated for those with no history. These results suggest sequential exposure to IMiDs across two LOTs to be mainly of concern for risk of severe cytopenias related to white blood cells, particularly neutrophils, and especially among those with recent histories.

In Aim 3, we sought to investigate the influence of specifying death as a censoring event versus

as a competing event on cumulative risk estimates. The Optum claims database, which reliably captures death, was used to create a cohort of 34,527 initiators of antihypertensive medications telmisartan (exposure) and ramipril (referent) who were at least 55 years old between 2003 and 2020, reflecting the eligibility criteria of a published real-world data emulation of a randomized clinical trial. We compared the 1-, 3-, and 5-year inverse probability of treatment-weighted cumulative risks of a composite outcome (myocardial infarction, stroke, and hospitalization for congestive heart failure) from models in which death was treated as a censoring event (cause-specific risk) versus competing event (sub-distribution risk). We examined whether the absolute difference between the two estimates depended on age strata and mortality rate in the claims-based analysis and in simulated cohorts. In the Optum cohort, differences in cumulative risks due to censoring of death, as compared to treating death as a competing event, increased with greater follow-up and increasing age, where event and mortality risks were higher. Simulation results from both a fully synthetically simulated and a plasmode-simulated cohort demonstrated the differences in cause-specific versus sub-distribution cumulative risks to increase with increasing mortality rate. These results suggest that researchers should consider baseline cohort mortality risk associated with treatment indication when deciding whether real-world data with incomplete death data can be used for cumulative risk estimation without concern.

Future Directions

There are several potential research questions generated based on the results of this dissertation that may be worthwhile to explore. The results of Aim 1 revealed limitations of the completeness and accuracy of gestational age information in the JMDC claims database given the lack of live birth delivery codes for the majority (60%) of the cohort. Missing delivery date information, coupled with suppression of infant birth dates and inaccessibility of ICD-10 codes with fifth level digits (where gestational week information would have been available), limits the

ability to finely estimate gestational timing, and therefore critical exposure windows, as needed for regulatory post-approval pregnancy safety studies. We suspect that for the majority (94%) of pregnancies that involve term deliveries, missing delivery and gestational timing information will result in only minor shifts of the exposure window. However, were an extremely preterm birth to lack codes related to both delivery and gestational timing, the estimated exposure window could be shifted so much as to have zero overlap with the true exposure window. Future work may explore methods to assign pregnancy onset and delivery dates so that *in utero* exposure windows can be defined more precisely. In particular, as our analysis identified pregnancy and delivery episodes based on diagnosis codes alone (which refer to the condition or disease being treated), but did not incorporate procedure codes (which refer to what was done or given to a patient in the inpatient setting, such as surgeries and medication administrations). Future studies may examine how including procedure codes may aid in estimation of delivery date and gestational age, especially for the nearly 60% of females in this cohort who were missing delivery diagnosis codes.

Finally, the population of unlinked pregnant people in the JMDC claims database is expected to be a combination of (a) mothers whose liveborn infants are covered by a different health insurer, (b) pregnant people whose pregnancy ended in a spontaneous abortion or stillbirth, and (c) females who did not experience a pregnancy during the study period. Our analyses did not explore the distribution of these groups within this population and therefore future work may query the unlinked pregnant people for diagnosis codes indicating the occurrence of spontaneous abortion and stillbirth to better understand this population.[110]

In Aim 2, within the IMiD exposure group, an individual could have been exposed to lenalidomide, pomalidomide, or thalidomide, each of which may be associated with a different risk of developing cytopenias.[128, 129, 135-148] Furthermore, patients may receive different doses of these drugs, in different combinations with other drug classes, which may also contribute to

differential cytopenia risk.[187] There may also be treatment-related outcome variance among those unexposed to IMiDs due to the differential cytopenia risks associated with other mutliple myeloma treatment drug classes (e.g., protesaome inhibitors, chemotherapy).[187, 207-211] These considerations may contribute to violations of counterfactual model sequential consistency.[206] Future analyses may consider more precisely defined exposure and active comparator definitions (e.g., drugs, combinations, and doses) to address potential issues with consistency.

Additionally, we considered the possibility that the treatment center where care was received could be a determinant of treatment choice and a proxy for socioeconomic cytopenia risk factors. For this reason, sensitivity analyses were performed in which patients were clustered within treatment centers, but the results of these multilevel models were not different from those of the main analyses. Future work may examine the impact of the healthcare system, at the level of the treatment center as well as the physician, on prescribing patterns and cytopenia risks among multiple myeloma patients.

In Aim 3, across the Optum overall and age-stratified analyses, as well as the simulated cohorts, the differences in the cause-specific versus sub-distribution models were similar for the telmisartan and ramipril groups, such that the resulting difference in the risk differences were quite small. We suspect this observation is due to the similar mortality and censoring rates of the two treatment groups. Future work may examine how differentially varying the mortality rates of the treatment groups (i.e., varying the association between exposure and the competing event) to make the mortality and censoring rates dissimilar may impact the difference in the cause-specific versus sub-distribution risk differences.

Additionally, the simulated cohorts allowed us to examine the influence on resulting cumulative risk estimates of mortality rate specifically, while maintaining outcome and censoring rates, which may not have been the case in the age-stratified Optum analyses. Additional exploratory analyses manipulated the relationships that an exogenous variable had with death and with

disenrollment, which likely resulted in an increased difference in cumulative risks from cause-specific versus sub-distribution models via its relative impacts on the mortality and disenrollment rates. These results suggested the difference in cumulative risks due to censoring on a competing event to be driven not only by the rate of the competing event, but also by this rate relative to the rate of other censoring events. Future work may consider how the ratio of competing events to censoring events may impact differences in cumulative risks and how quantitative bias analyses using estimations of this ratio may be used to adjust for such differences when true death information is incomplete or unavailable.[229]

Conclusions

Overall, by demonstrating the situations in which evidence from routine healthcare delivery services may be used to generate valid answers to comparative safety and effectiveness questions, this dissertation serves to promote the advancing of pharmacoepidemiologic methods and the understanding of appropriate uses for real-world data, which has important implications for ensuring the delivery of valid treatment information to patients, providers, and regulators. Patients and providers rely on the accuracy of regulatory decisions regarding the approval and labeling of medications as they reach shared decisions about treatments, with the goal of ensuring patients receive safe and effective care to alleviate disease burden and improve quality of life. Regulatory agencies have historically relied on clinical trial data for decision-making, especially for informing medication efficacy, but have been increasingly exploring approaches for supplementing such information with real-world data. The passing of the 21st Century Cures Act in December 2016 required FDA to evaluate the role of real-world data in supporting regulatory decision-making.[27] Since this legislation, several frameworks have been published by FDA, as well as by regulatory agencies in Canada, Europe, and Asia, describing how real-world evidence may be properly integrated in regulatory decision-making.[53,

[54, 257] Each aim of this dissertation addressed a distinct methodological challenge that epidemiologists in the pharmaceutical setting face with regards to using real-world data, which hinder its credibility for use in decision-making, including fitness for regulatory purpose of real-world databases, non-randomized allocation of drug products, and missing information, especially as it relates to outcome and competing event data.[23-26] As was demonstrated, appropriate selection of a data source that completely and accurately records all critical data elements and the implementation of high-quality study design techniques and rigorous analytical methods can combat the challenges that threaten the validity of observational pharmacoepidemiology studies using real-world data. With such methods, we can inform trustworthy uses of fit-for-purpose real-world data for regulatory and clinical decision-making, which ultimately supports the delivery of valid and timely treatment information to patients and providers.

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