Annals of Internal Medicine ORIGINAL RESEARCH

# Adverse Effects of Low-Dose Methotrexate

## A Randomized Trial

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**Background:** Low-dose methotrexate (LD-MTX) is the most commonly used drug for systemic rheumatic diseases worldwide and is the recommended first-line agent for rheumatoid arthritis. Despite extensive clinical use for more than 30 years, few data on adverse event (AE) rates derive from randomized, placebo-controlled trials, where both causality and magnitude of risk can be inferred.

**Objective:** To investigate AE rates, risk, and risk differences comparing LD-MTX versus placebo.

**Design:** Prespecified secondary analyses of a double-blind, placebo-controlled, randomized trial. (ClinicalTrials.gov: NCT01594333)

**Setting:** North America.

**Participants:** Adults with known cardiovascular disease and diabetes or metabolic syndrome.

**Intervention:** Random allocation to LD-MTX (≤20 mg/wk) or placebo. All participants received folic acid, 1 mg/d, 6 days per week.

**Measurements:** Risks for specific AEs of interest, as well as for all AEs, were compared across treatment groups after blinded adjudication.

**Results:** After an active run-in period, 6158 patients were enrolled and 4786 randomly assigned to a group; median follow-up was 23 months and median dosage 15 mg/wk. Among the randomly assigned participants, 81.2% were male, median age was 65.7 years, and median body mass index was 31.5 kg/m$^2$. Of 2391 participants assigned to LD-MTX, 2080 (87.0%) had an AE of interest, compared with 1951 of 2395 (81.5%) assigned to placebo (hazard ratio [HR], 1.17 [95% CI, 1.10 to 1.25]). The relative hazards of gastrointestinal (HR, 1.91 [CI, 1.75 to 2.10]), pulmonary (HR, 1.52 [CI, 1.16 to 1.98]), infectious (HR, 1.15 [CI, 1.01 to 1.30]), and hematologic (HR, 1.15 [CI, 1.07 to 1.23]) AEs were elevated for LD-MTX versus placebo. With the exception of increased risk for skin cancer (HR, 2.05 [CI, 1.28 to 3.28]), the treatment groups did not differ in risk for other cancer or mucocutaneous, neuropsychiatric, or musculoskeletal AEs. Renal AEs were reduced in the LD-MTX group (HR, 0.85 [CI, 0.78 to 0.93]).

**Limitation:** The trial was done in patients without rheumatic disease who tolerated LD-MTX during an active run-in period.

**Conclusion:** Use of LD-MTX was associated with small to moderate elevations in risks for skin cancer and gastrointestinal, infectious, pulmonary, and hematologic AEs, whereas renal AEs were decreased.

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Low-dose methotrexate (LD-MTX) serves as the cornerstone treatment and first-line medication in rheumatoid arthritis and is used by millions of patients worldwide (1). Dosages for rheumatoid arthritis are typically 10 to 25 mg/wk, much lower than those for cancer. The drug has been used in rheumatoid arthritis for more than 30 years, and studies have demonstrated reduced symptoms, less joint damage, synergistic benefits with biologic treatments, and possible mortality benefits (2–7). It is also widely used in other systemic rheumatic diseases, such as psoriatic arthritis, dermatomyositis, and systemic lupus erythematosus (8–10).

With decades of clinical use, LD-MTX has been associated with many toxicities, including hematologic (11–13), malignant, gastrointestinal (hepatic, nausea, and others) (14–22), pulmonary (23, 24), infectious (25–27), mucocutaneous (28, 29), renal (30), neuropsychiatric (31), and musculoskeletal (32) events. For example, anemia, thrombocytopenia, and leukopenia were reported in 3% to 10% of patients using LD-MTX during the 1980s and 1990s (11, 13, 33). Folic acid supplementation became routine in the late 1990s, but its effect on bone marrow toxicity and cytopenias is not clear (34). The effect of LD-MTX on cancer risk is unknown. High-dose MTX is widely used to treat various types of cancer, but observational data in patients with rheumatoid arthritis using LD-MTX show elevated standardized incidence ratios for any cancer, melanoma, lung cancer, and non-Hodgkin lymphoma (35). In addition, several other epidemiologic studies have found an association between LD-MTX use and increased risk for skin cancer (35, 36).

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Liver toxicity associated with LD-MTX is a major concern for clinicians and patients and can result in cirrhosis; thus, it prompts recommendations to conduct liver testing approximately every 8 to 12 weeks (37). These recommendations are based on the observation that persistent liver test abnormalities are almost always seen before major hepatic toxicity, such as cirrhosis (38). Although abnormal results on liver tests may be the first evidence of a potential problem, most such results represent innocuous fluctuations and normalize with little or no manipulation of LD-MTX dosage. No trials have blindly adjudicated hepatic-related adverse events (AEs). In contrast to the relatively uncommon outcome of cirrhosis, gastrointestinal intolerance is considered common with LD-MTX use, even with contemporary folic acid supplementation. A recent systematic review reported that 52 of 174 patients (30%) using LD-MTX had nausea or gastrointestinal upset (39).

Low-dose MTX may induce pulmonary AEs, such as cough and dyspnea (40). Hypersensitivity pneumonitis due to LD-MTX is believed to be relatively rare and is characterized by fever, shortness of breath, eosinophilia, and interstitial lung abnormalities on chest imaging; some cases progress to permanent lung damage (41, 42). Prior studies suggest that pneumonitis occurs in 0.1% to 1% of patients using LD-MTX (43). However, systemic rheumatic diseases may have pulmonary manifestations, such as interstitial lung disease, that are unrelated to LD-MTX and pose a challenge for determining causality (44). In addition, LD-MTX may increase risk for infection because of its immunosuppressive effects (26).

Prior studies of LD-MTX toxicity have been based on rheumatic disease cohorts in which all participants received treatment; thus, previous observational studies have been limited by lack of a placebo control group. In addition, most prior placebo-controlled trials had a small sample size and short duration, and routine folic acid supplementation was uncommon (45). Prior studies have also grouped all AEs to increase statistical power, but this limits interpretation.

To avoid these issues, we blindly adjudicated AEs on the basis of standardized clinical criteria and record review and formally evaluated rates associated with LD-MTX use in the setting of a large, contemporary, randomized, double-blind, placebo-controlled trial that enrolled men and women with cardiovascular disease and either type 2 diabetes or metabolic syndrome. We prespecified the current analyses and the LD-MTX toxicity end points assessed.

## METHODS

### Study Population and Design

CIRT (Cardiovascular Inflammation Reduction Trial) was a randomized, double-blind, placebo-controlled trial with enrollment goals based on a target number of cardiovascular outcomes. It was prematurely halted because of a lack of efficacy in the primary outcome of myocardial infarction, stroke, or death due to cardiovascular events (46). The trial enrolled patients starting in April 2013; study drug therapy was terminated in April 2018, and final safety visits were made in December 2018. Alongside CIRT, we did the current prospective study of prespecified and adjudicated AEs (1). The primary study population was the randomized CIRT cohort (**Appendix Figure**, available at Annals.org), but we also included participants from the active LD-MTX run-in phase as part of sensitivity analyses. Patients with known systemic rheumatic disease were excluded from CIRT. All potentially eligible patients were required at entry to have had a known myocardial infarction or multivessel obstructive coronary artery disease that had been clearly demonstrated, as well as type 2 diabetes or metabolic syndrome. **Appendix Table 1** (available at Annals.org) gives a full list of selection criteria.

All participants who met selection criteria and consented were entered into an active run-in period of 5 to 8 weeks, during which all were given LD-MTX. The dosage was uptitrated from 5 to 15 mg/wk over the run-in period; patients were seen after 2 to 3 weeks to assess for possible AEs, and laboratory assessment at the end of the run-in period assisted in determining tolerability of LD-MTX. Participants who successfully completed the active 5- to 8-week run-in phase with minimal adverse effects and sufficient adherence were randomly assigned in a 1:1 ratio to receive either oral LD-MTX or placebo; no subcutaneous dosing was used. The initial weekly dosage after randomization was 15 mg on 1 day per week and 1 mg of folic acid on the 6 other days. After 16 weeks, if all safety criteria had been met, dosage of the study drug (LD-MTX or placebo) was increased to its maximum, 20 mg/wk. During follow-up, participants who had an AE were eligible to keep receiving the study drug if the event was deemed reversible and did not put the participant at undue risk for future LD-MTX toxicity. The study drug was withdrawn but follow-up continued if participants had significant and unexplained chronic abnormalities on liver testing, myelosuppression, chronic infections, cancer (except for nonmelanoma skin cancer and localized prostate cancer), interstitial lung abnormalities, or newly diagnosed chronic kidney disease of stage 3 or 4. Study drug therapy was discontinued for patients who developed systemic rheumatic disease ($n$ = 10), for which LD-MTX or other immunosuppressive agents may be indicated. It was also discontinued for participants who developed a confirmed primary cardiovascular end point.

Using a central, blinded, computerized algorithm for drug dosing, we reduced dosages of the study drug or increased those of folic acid in both groups in response to certain mild toxicities, as is commonly done in routine practice. For example, participants who noted mouth pain or alopecia would have their dosage of the study drug reduced (for example, from 20 to 15 mg/wk) and folic acid increased (for example, from 1 to 2 mg/d for 6 days each week). Laboratory assessments were done at study visits every 4 to 12 weeks.

### Identification and Adjudication of AEs

We identified all potential AEs of interest (the **Supplement** [available at Annals.org] gives adjudication

forms, and a list is in the following paragraph), regardless of whether the site investigator believed that the AE was related to the study drug. Potential AEs were identified from several sources, such as routine visit and AE case report forms, reasons given by the site for a temporary or permanent withdrawal of the study drug, and central laboratory monitoring values.

We prespecified AEs of interest that prior literature had suggested were associated with LD-MTX; these AEs were adjudicated by study physicians blinded to randomization group using standardized forms based on previously published criteria (47–50). The **Supplement** gives details of the adjudication process and a full list of AEs. These events included gastrointestinal (hepatic and other), pulmonary, infectious, hematologic (hemorrhage and cytopenias), malignant, mucocutaneous (skin and oral), renal (acute kidney injury or nephrolithiasis), neuropsychiatric, and musculoskeletal AEs. Identification of potential AEs of interest that required adjudication triggered a record request from the participant's site. Information was requested before adjudication moved forward. If initial adjudication showed the need for specific information that had not been provided by the site, up to 3 additional requests were made.

The malignant AEs included all cancer but excluded premalignant diagnoses. Using a standardized form (**Supplement**), a hematology-oncology subspecialist (N.B.) supervised the blinded adjudication based on medical records. Cancer outcomes were considered definite if pathology reports noted malignancy, probable if treatment of cancer was documented but no definite pathology was available, and possible if cancer was mentioned but no pathology or cancer treatment was described in the medical record.

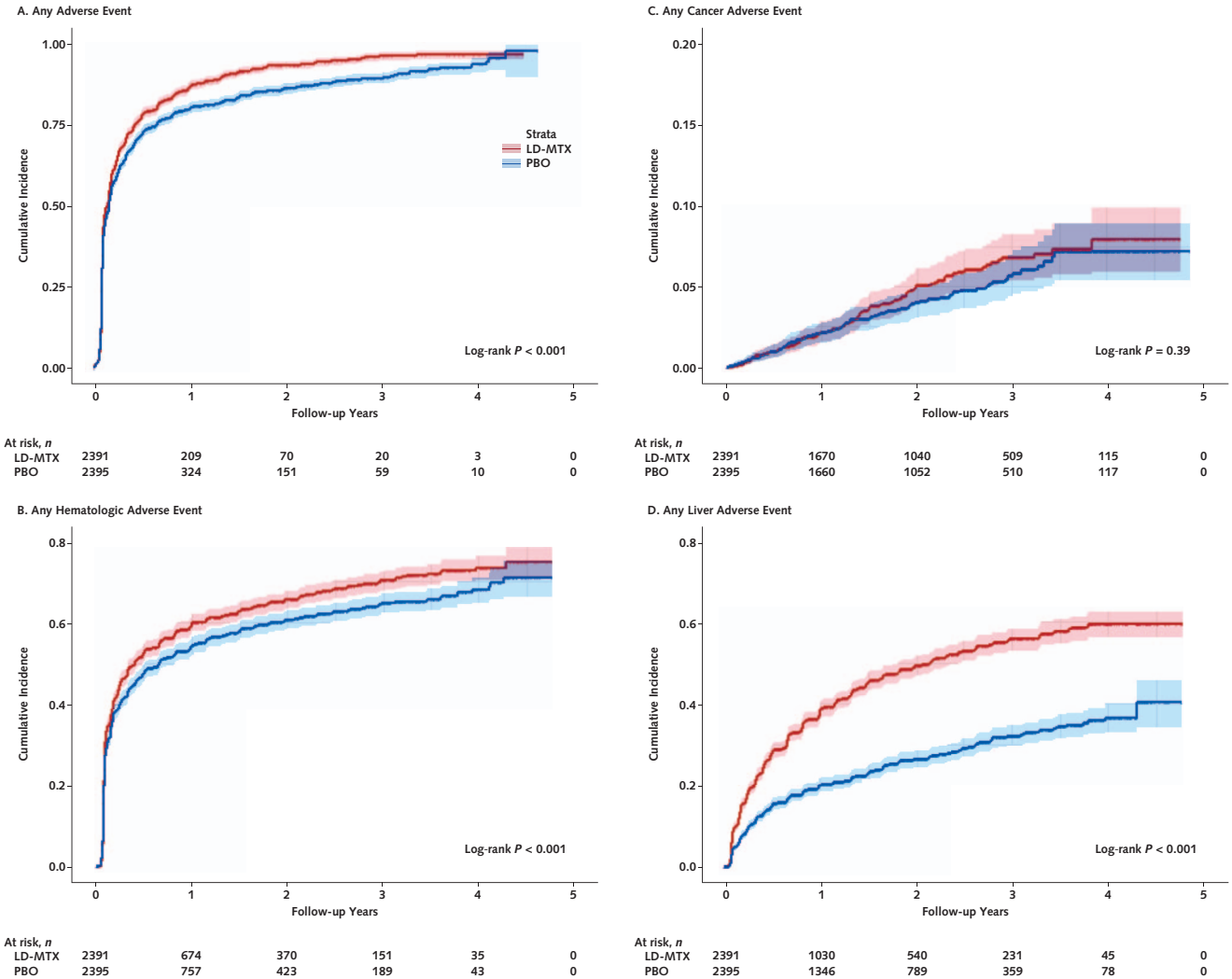
A hepatologist (A.R.) guided the blinded adjudication of gastrointestinal and liver AEs using a standardized form (**Supplement**). Liver test abnormalities were categorized on the basis of the upper limits of normal (ULNs) from national reference laboratories. The ULN for aspartate aminotransferase (AST) was 35 U/L (men and women); for alanine aminotransferase, it was 29

***Table 1.*** Baseline Characteristics of Randomized and Nonrandomized Populations in CIRT*

| Characteristic | Randomized Population | | Nonrandomized Population ($n$ = 1372)† |
|---|---|---|---|
| | Low-Dose Methotrexate ($n$ = 2391) | Placebo ($n$ = 2395) | |
| Female sex | 461 (19.3) | 437 (18.2) | 321 (23.4) |
| Median age at enrollment date (IQR), *y* | 65.5 (59.5–71.6) | 65.9 (59.7–71.6) | 65.6 (58.6–72.0) |
| Race | | | |
| White | 2008 (84.0) | 2059 (86.0) | 1118 (81.5) |
| Black or African American | 194 (8.1) | 156 (6.5) | 135 (9.8) |
| Asian | 89 (3.7) | 92 (3.8) | 54 (3.9) |
| American Indian or Alaska Native | 6 (0.25) | 7 (0.29) | 4 (0.29) |
| Native Hawaiian or other Pacific Islander | 4 (0.17) | 6 (0.25) | 5 (0.36) |
| Multiple | 15 (0.63) | 9 (0.38) | 8 (0.58) |
| Other | 75 (3.1) | 66 (2.8) | 48 (3.5) |
| Diabetes | 1620 (67.8) | 1615 (67.4) | 957 (69.8) |
| Metabolic syndrome | 1603 (67.0) | 1572 (65.6) | 900 (65.6) |
| Hyperlipidemia | 2053 (85.9) | 2050 (85.6) | 962 (70.1) |
| Hypertension | 2153 (90.0) | 2169 (90.6) | . . . |
| Current cigarette use | 267 (11.2) | 270 (11.3) | . . . |
| Alcohol use | | | |
| Rarely or never | 1487 (62.2) | 1473 (61.5) | . . . |
| ≤1 drink/wk | 514 (21.5) | 520 (21.7) | . . . |
| >1 drink/wk | 390 (16.3) | 402 (16.8) | . . . |
| Median eGFR (IQR), *mL/min/1.73 m²* | 81.2 (67.8–95.3) | 80.9 (66.4–95.5) | . . . |
| Median body mass index (IQR), *kg/m²* | 31.6 (28.1–35.7) | 31.3 (28.0–35.5) | 31.2 (27.8–35.3) |
| Mean study drug dosage (SD), *mg/wk*‡ | 14.9 (4.5) | 15.3 (4.3) | – |
| Statin use | 2062 (86.2) | 2052 (85.7) | 976 (71.1) |
| Aspirin use | 1861 (77.8) | 1807 (75.4) | 875 (63.8) |
| Insulin use | 515 (21.5) | 535 (22.3) | 297 (21.6) |
| Oral corticosteroid use | 27 (1.1) | 22 (0.9) | 7 (0.5) |
| Respiratory medication use | 273 (11.4) | 291 (12.2) | 164 (12.0) |
| Noncorticosteroid inhaler | 186 (7.8) | 212 (8.9) | 120 (8.7) |
| Corticosteroid inhaler | 42 (1.8) | 55 (2.3) | 22 (1.6) |
| Combination inhaler | 136 (5.7) | 135 (5.6) | 88 (6.4) |
| Oral and intravenous medications for respiratory conditions | 48 (2.0) | 54 (2.3) | 19 (1.4) |
| Median SF-36 general health subscore (IQR) | 60 (45–75) | 60 (45–75) | 55 (35–70) |
| Median CES-D-10 score (IQR) | 5 (2–9) | 5 (2–8) | 6 (3–10) |

CES-D-10 = 10-item Center for Epidemiologic Studies Depression Scale; CIRT = Cardiovascular Inflammation Reduction Trial; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SF-36 = Short Form-36 Health Survey.
* Values are numbers (percentages) unless otherwise indicated.
† Includes participants who received open-label methotrexate during the prerandomization run-in phase but were not ultimately assigned to a group. The ellipsis (. . .) signifies that >90% of that variable was missing for non–randomly assigned participants because these were primarily collected at the time of randomization.
‡ Refers to the postrandomization period.

***Figure.*** Cumulative incidence plots with 95% CIs for the modified intention-to-treat analyses, censoring 180 d after the last dose of study drug.

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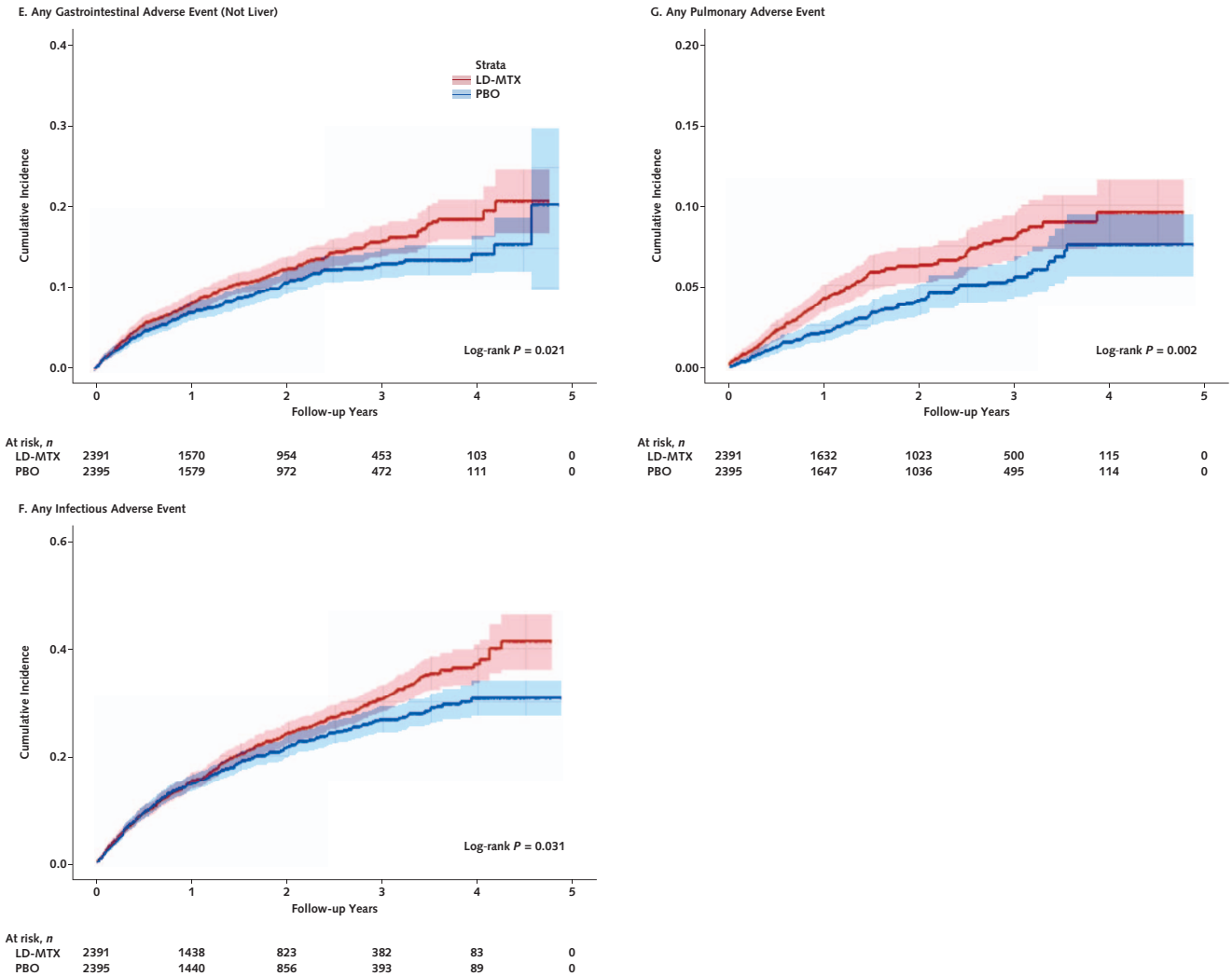
U/L for women and 46 U/L for men. Mild elevations in the liver test results were defined as more than 1 to 2 times ULN, moderate elevations as more than 2 to 3 times ULN, and severe elevations as more than 3 times ULN. We also examined the frequency of repeated abnormal results on liver tests (that is, elevations in 5 of 9 consecutive AST measurements); prior work has suggested this as a risk factor for cirrhosis (20). The other gastrointestinal AEs included nausea, vomiting, or diarrhea (all categorized together); abdominal pain without nausea, vomiting, or diarrhea; gallstones or cholecystitis; and "other," which included small-bowel obstruction, constipation, pancreatitis, and other less common gastrointestinal conditions.

An infectious diseases specialist (S.P.H.) guided the adjudication of infectious AEs. At each study visit, current and recent infections and infectious symptoms were queried. If reports were positive, we obtained medical records to classify the presence, dates of onset and resolution, type, likelihood, and severity of infection. We defined infection likelihood using symptoms of infection, such as fever: In possible infections, symptoms were not treated with systemic antimicrobial agents; in probable infections, they were treated with systemic (nontopical) antimicrobial agents; and in definite infections, symptoms coexisted with microbiological evidence, an infectious disease consultant had an impression of infection, or radiographic evidence was present without other more likely causes. Infections were broadly grouped into the following categories on the basis of the predominant clinical manifestations: upper respiratory infection or viral syndrome; skin or soft tissue infection; pneumonia; ear, eye, nose, throat, or dental infection; genitourinary infection; gastrointestinal infection; shingles; bone or joint infection; candidiasis; sepsis; and "not otherwise specified."

***Figure***–Continued.




The log-rank test was used to estimate the *P* value. LD-MTX = low-dose methotrexate; PBO = placebo. **A.** All adverse events of interest, with laboratory abnormalities included. **B.** Any hematologic adverse events, with laboratory abnormalities included. **C.** All cancer adverse events. **D.** All liver adverse events, with laboratory abnormalities included. **E.** All gastrointestinal adverse events, excluding liver and liver test abnormalities. **F.** All infectious adverse events. **G.** All pulmonary adverse events.

Possible pulmonary AEs were blindly adjudicated using a standardized form (**Supplement**) under the guidance of a specialist in rheumatology and critical care medicine (P.F.D.). Possible pulmonary AEs were elicited from participants at every study visit, and medical records were obtained to classify the presence, dates of onset and resolution, type, likelihood, and severity of events. Possible pulmonary AEs were defined by new respiratory symptoms with normal or no diagnostic testing obtained. Probable pulmonary AEs had new symptoms with abnormalities on diagnostic testing. Definite pulmonary AEs had new symptoms and diagnostic test abnormalities, and symptoms improved when the patient was not receiving the study drug. Pulmonary AEs were broadly grouped into the following categories: bronchitis, shortness of breath, cough, chronic obstructive pulmonary disease or asthma flare, pneumonitis, and "not otherwise specified."

Any pulmonary AE with mention of pulmonary fibrosis, interstitial lung disease, or ground-glass opacities was also reviewed for the possibility of pneumonitis. We used previously published criteria to classify the probability of pneumonitis due to LD-MTX (47). Possible pneumonitis required at least 4 of the following criteria: fever, tachypnea or cough, radiologic evidence of interstitial or alveolar abnormalities, leukocytosis, and negative results on blood or sputum cultures. Probable cases additionally required clinical suspicion of having been induced by LD-MTX. Definite cases additionally required strong suspicion of having been induced by LD-MTX and symptom improvement after study drug withdrawal.

For AEs that are primarily subjective symptoms, such as nausea, abdominal pain, and alopecia, further records were not pursued and the description on the case report form was used for adjudication. After reviewing available

*Table 2.* Risks Comparing AEs for Methotrexate Versus Placebo During the Randomized Phase of CIRT*

| AE Type | Low-Dose Methotrexate ($n$ = 2391) | | | Placebo ($n$ = 2395) | | | Risk Difference (95% CI)‡ | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | | |
| **AEs of interest, including laboratory abnormalities** | 2080 (87.0) | 241 (230 to 251) | 0.96 (0.95 to 0.97) | 1951 (81.5) | 172 (164 to 179) | 0.89 (0.88 to 0.91) | 0.07 (0.05 to 0.09) | 1.17 (1.10 to 1.25) |
| Mild | 2023 (84.6) | 212 (203 to 221) | 0.95 (0.93 to 0.96) | 1890 (78.9) | 153 (146 to 160) | 0.87 (0.85 to 0.89) | 0.08 (0.05 to 0.10) | 1.18 (1.11 to 1.26) |
| Moderate | 772 (32.3) | 22.0 (20.4 to 23.5) | 0.44 (0.41 to 0.47) | 661 (27.6) | 18.2 (16.8 to 19.5) | 0.37 (0.35 to 0.40) | 0.07 (0.03 to 0.10) | 1.19 (1.08 to 1.33) |
| Severe | 222 (9.3) | 5.1 (4.4 to 5.8) | 0.13 (0.12 to 0.15) | 155 (6.5) | 3.5 (2.9 to 4.1) | 0.10 (0.08 to 0.11) | 0.04 (0.01 to 0.06) | 1.46 (1.19 to 1.79) |
| **AEs of interest, excluding laboratory abnormalities** | 1012 (42.3) | 33.1 (31.0 to 35.1) | 0.54 (0.52 to 0.57) | 901 (37.6) | 28.1 (26.3 to 29.9) | 0.49 (0.46 to 0.52) | 0.05 (0.02 to 0.09) | 1.16 (1.06 to 1.27) |
| Mild | 612 (25.6) | 16.5 (15.2 to 17.8) | 0.35 (0.33 to 0.38) | 512 (21.4) | 13.5 (12.3 to 14.7) | 0.28 (0.26 to 0.31) | 0.07 (0.04 to 0.10) | 1.21 (1.08 to 1.37) |
| Moderate | 530 (22.2) | 13.7 (12.6 to 14.9) | 0.30 (0.28 to 0.33) | 475 (19.8) | 12.1 (11.0 to 13.2) | 0.27 (0.25 to 0.30) | 0.03 (0.00 to 0.06) | 1.13 (1.00 to 1.28) |
| Severe | 152 (6.4) | 3.4 (2.9 to 4.0) | 0.09 (0.08 to 0.11) | 125 (5.2) | 2.8 (2.3 to 3.3) | 0.08 (0.07 to 0.10) | 0.01 (−0.01 to 0.03) | 1.22 (0.97 to 1.55) |
| **Coded AEs§** | 2156 (90.2) | 305 (292 to 318) | 0.97 (0.96 to 0.98) | 2076 (86.7) | 226 (217 to 236) | 0.94 (0.92 to 0.95) | 0.04 (0.02 to 0.06) | 1.14 (1.08 to 1.22) |
| MedDRA events, including laboratory abnormalities | 2155 (90.1) | 289 (277 to 301) | 0.97 (0.95 to 0.98) | 2071 (86.5) | 214 (205 to 224) | 0.93 (0.91 to 0.94) | 0.04 (0.02 to 0.06) | 1.15 (1.08 to 1.22) |
| MedDRA events, excluding laboratory abnormalities | 1483 (62.0) | 65.8 (62.5 to 69.1) | 0.74 (0.72 to 0.77) | 1432 (59.8) | 62 (58 to 65) | 0.73 (0.71 to 0.75) | 0.02 (−0.02 to 0.05) | 1.06 (0.98 to 1.14) |

AE = adverse event; CIRT = Cardiovascular Inflammation Reduction Trial; MedDRA = Medical Dictionary for Regulatory Activities.
* These numbers are based on the modified intention-to-treat analyses (see text for details).
† Includes first events of a given type; percentages refer to the number of participants with a given AE divided by all participants in the respective treatment group. The first mild, moderate, and severe event, as well as the first of each type of AE, were included.
‡ Based on the 3-y cumulative incidence percentage of risk.
§ Includes MedDRA-coded events, not just the adjudicated events of interest.

medical records and information from the sites, we classified AEs of interest by likelihood (possible, probable, or definite) and severity (mild, moderate, or severe). Some AEs of interest were not categorized as possible, probable, or definite but rather "reported" by patients or "confirmed" by medical records; the reported events were considered possible and the confirmed events definite. The primary outcome included probable and definite events (and those confirmed by medical records) and excluded possible events. Secondary outcomes examined AEs by likelihood and severity. We defined AE severity as mild, moderate, or severe on the basis of prespecified thresholds (Supplement). Laboratory assessments, including complete blood counts (anemia, thrombocytopenia, and leukopenia), liver tests (elevated levels of AST or alanine aminotransferase), and serum creatinine measurements (translated into estimated glomerular filtration rate [eGFR] using the MDRD [Modification of Diet in Renal Disease] equation), were done at central laboratories approximately every 8 weeks during follow-up. We specified thresholds for abnormal laboratory values according to standard definitions (46).

We also defined a secondary outcome using not only the AEs of interest but all AEs noted on the case report forms; this improved comparability with the main CIRT analyses (46). For this secondary analysis, AEs were categorized according to MedDRA (Medical Dictionary for Regulatory Activities) rather than the adjudicated categories (51). Although the adjudication process described earlier provides a more sensitive and specific measure for the events of interest, we chose to use the MedDRA standardized method across all event types for this secondary outcome to give numbers comparable to those in the original trial report.

## Statistical Analysis

Per the prespecified analysis plan, the primary analysis examined the occurrence of any prespecified, adjudicated AE of interest and laboratory abnormalities in the randomized study cohort. Thus, it excluded participants who did not complete the active run-in phase. The primary analyses considered all first events after randomization within each category by severity or subtype of event, depending on the analysis; thus, only the first AE of a given type was included, and participants could contribute AEs in several categories. The primary analysis of the frequency and relative rates of AEs followed a modified intention-to-treat strategy (sometimes called an "as-treated" approach). Because approximately 19% of participants prematurely discontinued treatment after randomization and may have been followed for many months after treatment discontinuation, we followed participants from the time of randomization through 180 days after the known date of treatment discontinuation, as noted by the study site. This modified intention-to-treat strategy is commonly used for safety analyses. A secondary analysis used an intention-to-treat approach without censoring at study drug withdrawal.

We constructed cumulative incidence curves for the AE end points. These curves examined the time to first AE for the LD-MTX and placebo groups separately. Statistical significance was judged using a likelihood ratio test based on proportional hazards regression models, adjusted for the following stratifying variables: time since qualifying cardiovascular event (≥6 months vs. <6 months), type of prior cardiovascular event (myocardial infarction vs. multivessel coronary artery disease), and diabetes mellitus versus metabolic syndrome alone at

baseline. The 3-year cumulative incidence percentages of risk were estimated from the Kaplan–Meier survival curves, and proportional hazards models were fitted separately for any AE and then for each AE of interest. The null hypothesis being tested was no association between outcomes and assignment to LD-MTX versus placebo, and the exact method was used to handle ties. The proportional hazards assumption was tested using Schoenfeld residuals (52). The differences in the 3-year cumulative incidence risk between LD-MTX and placebo were calculated.

Several secondary analyses were prespecified, but we did not correct *P* values for multiple comparisons; instead, we show the 95% CIs. First, the primary outcome was analyzed using an intention-to-treat approach, including all time from randomization until the first of any of the following: AE, death, end of trial, withdrawal of consent, or termination of study. Second, the modified intention-to-treat analysis was done using 0 and 90 days after termination of treatment as alternative censoring dates. Third, possible AEs were included along with the probable and definite events. Fourth, the hazards of specific types of AEs of interest were estimated using the same proportional hazards models described earlier for the modified intention-to-treat analysis. Fifth, the frequency and relative rates of mild, moderate, and severe events were estimated separately. Sixth, the frequency and relative risk for any AE (including the MedDRA events, which were reported by sites but not adjudicated) were also estimated. Finally, the frequency of AEs during the prerandomization period was assessed, and logistic regression was used to examine factors associated with participants who were not randomly assigned.

All analyses were done in SAS, version 9.4 (SAS Institute).

### Role of the Funding Source

The National Institutes of Health was aware of the study design and study conduct and approved the analysis plan, but it had no role in the decision to publish the results.

## RESULTS

A total of 9321 persons were screened for CIRT, and 6158 entered the prerandomization phase (**Appendix Figure**). Of those who participated in the active run-in period, 4786 (77.7%) were eventually assigned to a group and followed for a median of 23 months receiving the study drug, with similar follow-up in both groups. **Table 1** shows the characteristics of the randomized groups. Age, sex, body mass index, tobacco use, alcohol use, frequency of diabetes, eGFR, and use of medications were similar across treatment groups. Patients who were not randomly assigned were more likely to be black, not use statins or aspirin, and have lower self-reported general health.

Of the 2391 participants in the LD-MTX group, 2156 (90.2%) had any AE and 2080 (87.0%) had an adjudicated AE of interest. Of the 2395 participants as-

***Table 3.*** Frequency and Relative Risks Comparing Hematologic and Cancer AEs for Methotrexate Versus Placebo During the Randomized Phase of CIRT*

| AE | Low-Dose Methotrexate (*n* = 2391) | | | Placebo (*n* = 2395) | | | Risk Difference (95% CI)‡ | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Events, *n* (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | Events, *n* (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | | |
| **Any hematologic event** | 965 (40.4) | 31.7 (29.7 to 33.7) | 0.95 (0.89 to 1.01) | 824 (34.4) | 25.6 (23.8 to 27.3) | 0.77 (0.72 to 0.82) | 0.18 (0.09 to 0.27) | 1.22 (1.11 to 1.34) |
| **Anemia** | 722 (30.2) | 20.9 (19.4 to 22.4) | 0.37 (0.35 to 0.40) | 555 (23.2) | 15 (13.8 to 16.3) | 0.30 (0.28 to 0.33) | 0.07 (0.04 to 0.11) | 1.36 (1.22 to 1.52) |
| Mild | 630 (26.4) | 17.7 (16.3 to 19.1) | 0.32 (0.30 to 0.35) | 485 (20.3) | 12.8 (11.6 to 13.9) | 0.26 (0.24 to 0.29) | 0.06 (0.03 to 0.09) | 1.36 (1.21 to 1.53) |
| Moderate | 110 (4.6) | 2.4 (2.0 to 2.9) | 0.07 (0.05 to 0.08) | 76 (3.2) | 1.7 (1.3 to 2.1) | 0.04 (0.03 to 0.06) | 0.02 (0.01 to 0.04) | 1.45 (1.08 to 1.94) |
| Severe | 10 (0.4) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 9 (0.4) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 1.10 (0.45 to 2.71) |
| **Thrombocytopenia** | 204 (8.5) | 4.7 (4.1 to 5.4) | 0.12 (0.10 to 0.14) | 256 (10.7) | 6.1 (5.4 to 6.9) | 0.14 (0.12 to 0.16) | −0.02 (−0.04 to 0.01) | 0.78 (0.65 to 0.93) |
| Mild | 202 (8.5) | 4.7 (4.0 to 5.3) | 0.12 (0.10 to 0.14) | 255 (10.6) | 6.1 (5.3 to 6.8) | 0.14 (0.12 to 0.16) | −0.02 (−0.04 to 0.01) | 0.77 (0.64 to 0.93) |
| Moderate | 2 (0.1) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.00) | 3 (0.1) | 0.1 (0.0 to 0.1) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.66 (0.11 to 3.96) |
| Severe | 0 (0.0) | 0.0 (0.0 to 0.0) | 0.00 (0.00 to 0.00) | 0 (0.0) | 0.0 (0.0 to 0.0) | 0.00 (0.00 to 0.00) | 0.00 (0.00 to 0.00) | – |
| **Leukopenia** | 220 (9.2) | 5.1 (4.4 to 5.8) | 0.12 (0.11 to 0.14) | 152 (6.3) | 3.5 (2.9 to 4.0) | 0.08 (0.07 to 0.10) | 0.04 (0.02 to 0.06) | 1.46 (1.19 to 1.80) |
| Mild | 204 (8.5) | 4.7 (4.1 to 5.4) | 0.12 (0.10 to 0.13) | 139 (5.8) | 3.2 (2.7 to 3.7) | 0.08 (0.06 to 0.09) | 0.04 (0.02 to 0.06) | 1.48 (1.19 to 1.84) |
| Moderate | 28 (1.2) | 0.6 (0.4 to 0.8) | 0.02 (0.01 to 0.03) | 19 (0.8) | 0.4 (0.2 to 0.6) | 0.01 (0.01 to 0.02) | 0.00 (0.00 to 0.01) | 1.47 (0.82 to 2.62) |
| **Cancer type** | | | | | | | | |
| Any cancer | 101 (4.2) | 2.2 (1.8 to 2.7) | 0.07 (0.06 to 0.08) | 89 (3.7) | 2.0 (1.6 to 2.4) | 0.06 (0.05 to 0.07) | 0.01 (−0.01 to 0.03) | 1.13 (0.85 to 1.51) |
| Skin | 53 (2.2) | 1.2 (0.8 to 1.5) | 0.04 (0.03 to 0.05) | 26 (1.1) | 0.6 (0.3 to 0.8) | 0.02 (0.01 to 0.03) | 0.02 (0.01 to 0.03) | 2.04 (1.28 to 3.26) |
| Solid tumor | 39 (1.6) | 0.8 (0.6 to 1.1) | 0.02 (0.02 to 0.03) | 49 (2.0) | 1.1 (0.8 to 1.4) | 0.03 (0.02 to 0.04) | −0.01 (−0.02 to 0.00) | 0.79 (0.52 to 1.20) |
| Lung | 10 (0.4) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 1.24 (0.49 to 3.13) |
| Head and neck | 0 (0.0) | 0.0 (0.0 to 0.0) | 0.00 (0.00 to 0.00) | 1 (0.0) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.00) | 0.00 (0.00 to 0.00) | – |
| Prostate | 10 (0.4) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.02) | 16 (0.7) | 0.3 (0.2 to 0.5) | 0.01 (0.01 to 0.02) | 0.00 (−0.01 to 0.00) | 0.62 (0.28 to 1.36) |
| Bladder | 7 (0.3) | 0.2 (0.0 to 0.3) | 0.00 (0.00 to 0.01) | 5 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 1.39 (0.44 to 4.40) |
| Breast | 2 (0.1) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.00) | 5 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.40 (0.08 to 2.06) |
| Kidney | 2 (0.1) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.01) | 4 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.49 (0.09 to 2.72) |
| Intestinal/colon | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.00 (0.00 to 0.01) | 10 (0.4) | 0.2 (0.1 to 0.4) | 0.01 (0.00 to 0.01) | 0.00 (−0.01 to 0.00) | 0.80 (0.32 to 2.01) |
| Hematologic | 6 (0.3) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 7 (0.3) | 0.2 (0.0 to 0.3) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.85 (0.29 to 2.51) |
| Other | 3 (0.1) | 0.1 (0.0 to 0.1) | 0.00 (0.00 to 0.01) | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 0.00 (−0.01 to 0.00) | 0.37 (0.01 to 1.39) |

AE = adverse event; CIRT = Cardiovascular Inflammation Reduction Trial.
* These numbers are based on the modified intention-to-treat analyses (see text for details).
† Includes first events of a given type; percentages refer to the number of participants with a given AE divided by all participants in the respective treatment group. The first mild, moderate, and severe event, as well as the first of each type of AE, were included.
‡ Based on the 3-y cumulative incidence percentage of risk.

*Table 4.* Frequency and Relative Risks Comparing Liver and Other Gastrointestinal AEs for Methotrexate Versus Placebo During the Randomized Phase of CIRT*

| AE | Low-Dose Methotrexate ($n$ = 2391) | | | Placebo ($n$ = 2395) | | | Risk Difference (95% CI)‡ | Hazard Ratio (95% CI)§ |
|---|---|---|---|---|---|---|---|---|
| | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | | |
| **Liver enzyme elevation** | 1042 (43.6) | 36.1 (33.9 to 38.3) | 0.56 (0.53 to 0.58) | 576 (24.1) | 15.6 (14.4 to 16.9) | 0.32 (0.29 to 0.34) | 0.24 (0.20 to 0.27) | 2.14 (1.93 to 2.37) |
| Mild | 1010 (42.2) | 34.4 (32.3 to 36.5) | 0.54 (0.51 to 0.57) | 559 (23.3) | 15.1 (13.8 to 16.3) | 0.31 (0.28 to 0.33) | 0.23 (0.20 to 0.27) | 2.12 (1.91 to 2.35) |
| Moderate | 187 (7.8) | 4.2 (3.6 to 4.9) | 0.12 (0.10 to 0.14) | 49 (2.0) | 1.1 (0.8 to 1.4) | 0.03 (0.02 to 0.04) | 0.09 (0.07 to 0.11) | 3.94 (2.87 to 5.39) |
| Severe | 69 (2.9) | 1.5 (1.2 to 1.9) | 0.04 (0.03 to 0.06) | 26 (1.1) | 0.6 (0.4 to 0.8) | 0.01 (0.01 to 0.02) | 0.03 (0.02 to 0.04) | 2.67 (1.70 to 4.19) |
| **Any liver pathology** | 13 (0.5) | 0.3 (0.1 to 0.4) | 0.01 (0.01 to 0.02) | 7 (0.3) | 0.2 (0.0 to 0.3) | 0.00 (0.00 to 0.01) | 0.01 (0.00 to 0.01) | 1.83 (0.73 to 4.55) |
| Cirrhosis | 5 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 0 (0.0) | 0.0 (0.0 to 0.0) | 0.00 (0.00 to 0.00) | 0.00 (0.00 to 0.00) | . . . |
| Nonalcoholic fatty liver disease | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.02) | 7 (0.3) | 0.2 (0 to 0.3) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.01) | 1.13 (0.41 to 3.08) |
| **Gastrointestinal** | | | | | | | | |
| Any | 273 (11.4) | 6.4 (5.7 to 7.2) | 0.16 (0.14 to 0.18) | 224 (9.4) | 5.2 (4.5 to 5.9) | 0.13 (0.12 to 0.15) | 0.03 (0.00 to 0.05) | 1.23 (1.03 to 1.47) |
| Mild | 118 (4.9) | 2.6 (2.2 to 3.1) | 0.07 (0.06 to 0.08) | 101 (4.2) | 2.3 (1.8 to 2.7) | 0.06 (0.05 to 0.07) | 0.01 (−0.01 to 0.02) | 1.17 (0.90 to 1.52) |
| Moderate | 132 (5.5) | 3.0 (2.4 to 3.5) | 0.08 (0.07 to 0.10) | 109 (4.6) | 2.4 (2.0 to 2.9) | 0.07 (0.05 to 0.08) | 0.01 (0.00 to 0.03) | 1.21 (0.94 to 1.56) |
| Severe | 53 (2.2) | 1.2 (0.8 to 1.5) | 0.03 (0.02 to 0.04) | 44 (1.8) | 1.0 (0.7 to 1.3) | 0.03 (0.02 to 0.04) | 0.00 (−0.01 to 0.01) | 1.20 (0.81 to 1.79) |
| By subcategory | | | | | | | | |
| Nausea, vomiting, or diarrhea | 174 (7.3) | 3.9 (3.4 to 4.5) | 0.10 (0.09 to 0.12) | 135 (5.6) | 3.1 (2.5 to 3.6) | 0.07 (0.06 to 0.09) | 0.03 (0.01 to 0.05) | 1.30 (1.03 to 1.63) |
| Abdominal pain | 74 (3.1) | 1.6 (1.3 to 2.0) | 0.05 (0.04 to 0.06) | 60 (2.5) | 1.3 (1.0 to 1.7) | 0.04 (0.03 to 0.05) | 0.01 (−0.01 to 0.02) | 1.23 (0.87 to 1.73) |
| Gallstones or cholecystitis | 22 (0.9) | 0.5 (0.3 to 0.7) | 0.01 (0.01 to 0.02) | 15 (0.6) | 0.3 (0.2 to 0.5) | 0.01 (0.00 to 0.01) | 0.01 (0.00 to 0.01) | 1.45 (0.74 to 2.83) |
| Other‖ | 42 (1.8) | 0.9 (0.6 to 1.2) | 0.02 (0.02 to 0.03) | 47 (2.0) | 1.0 (0.7 to 1.3) | 0.03 (0.02 to 0.04) | 0.00 (−0.02 to 0.01) | 0.89 (0.57 to 1.38) |

AE = adverse event; CIRT = Cardiovascular Inflammation Reduction Trial.
* These numbers are based on the modified intention-to-treat analyses (see text for details).
† Includes first events of a given type; percentages refer to the number of participants with a given AE divided by all participants in the respective treatment group. The first mild, moderate, and severe event, as well as the first of each type of AE, were included.
‡ Based on the 3-y cumulative incidence percentage of risk.
§ The ellipsis (. . .) refers to a hazard ratio that could not be estimated.
‖ Includes constipation, pancreatitis, small-bowel obstruction, weight loss, and "not otherwise specified."

signed to placebo, 2076 (86.7%) had any AE and 1951 (81.5%) had an adjudicated AE of interest. The relative rate of an AE of interest was 17% higher for those assigned to LD-MTX (hazard ratio [HR], 1.17 [95% CI, 1.10 to 1.25]) compared with placebo. The cumulative incidence curves for AEs (**Figure**) show an increased risk for overall AEs (log-rank $P < 0.001$). The frequency, relative rates, cumulative risk, and risk differences of mild, moderate, and severe events were estimated for both treatment groups (**Table 2**). We found similar increases across all severity ratings in relative rates for LD-MTX compared with placebo.

The relative rates of gastrointestinal (HR, 1.23 [CI, 1.03 to 1.47]), pulmonary (HR, 1.42 [CI, 1.14 to 1.77]), infectious (HR, 1.15 [CI, 1.01 to 1.30]), and hematologic (HR, 1.22 [CI, 1.11 to 1.34]) AEs were elevated for LD-MTX (**Tables 3** to **5**) compared with placebo. The treatment groups did not differ in risk for cancer overall (**Table 3**), but 53 participants (2.2%) in the LD-MTX group and 26 (1.1%) in the placebo group had skin cancer, for an HR of 2.04 (CI, 1.28 to 3.26). The risk for squamous cell skin cancer reached statistical significance (HR, 3.31 [CI, 1.63 to 6.71]). Risks for anemia (HR, 1.36 [CI, 1.22 to 1.52]) and leukopenia (HR, 1.46 [CI, 1.19 to 1.80]) were also elevated, but no increase was observed for thrombocytopenia (HR, 0.78 [CI, 0.65 to 0.93]).

Hepatic pathology was more common in the LD-MTX group (**Table 4**). Five cases of cirrhosis were seen in the primary, modified intention-to-treat analysis (rate, 0.11 cases [CI, 0.01 to 0.20 cases] per 100 person-years) versus none in the placebo group (exact test $P = 0.032$). Of note, at the baseline visit, none of the cirrhosis case patients reported ever using alcohol. The body mass indices were all in the obese range, except for 1; however, the mean body mass index for the trial was also in the obese range. All participants with cirrhosis had diabetes (vs. 68% overall in the trial), 3 had metabolic syndrome, and none reported tobacco use. The duration of LD-MTX use was only several months for 3 participants and several years for the others. All participants had 1 or more liver test abnormalities before the diagnosis of cirrhosis, but none had severe abnormalities. Three patients diagnosed with cirrhosis had repeated elevations in AST level, defined as 5 elevations out of 9 consecutive assessments; this is from a total of 139 participants who were randomly assigned to LD-MTX and had repeated AST elevations. No cases of cirrhosis developed in the 72 participants in the placebo group with this same abnormal pattern. One LD-MTX participant with cirrhosis died during follow-up, and cirrhosis was part of his cause of death. In addition to liver pathology, gastrointestinal AEs also increased (HR, 1.23 [CI, 1.03 to 1.47]).

Six patients (0.3%) in the LD-MTX group and 1 (0.04%) in the placebo group had possible pneumonitis (HR, 6.94 [CI, 0.85 to 56.0]; exact test $P = 0.044$); no cases could be considered probable or definite because too little information was provided. The cases in the LD-MTX group occurred between 2 and 27 months after randomization. All participants were men, none reported any history of tobacco use, and 2 died. In addition, when considering any pulmonary AE, we found an increased risk with LD-MTX (HR, 1.42 [CI, 1.14 to 1.77]). Finally, the risk for any infectious AE, pulmonary or otherwise, was elevated (HR, 1.15 [CI, 1.01 to 1.30]).

Renal AEs decreased among LD-MTX users (HR, 0.85 [CI, 0.78 to 0.93]). This reduction was driven pri-

marily by trends in eGFR: Final median eGFR was 79.1 mL/min/1.73 $m^2$ (interquartile range, 65.7 to 93.4 mL/min/1.73 $m^2$) for the LD-MTX group versus 77.2 mL/min/1.73 $m^2$ (interquartile range, 63.4 to 91.8 mL/min/1.73 $m^2$) for the placebo group (Kruskal–Wallis $P$ = 0.001).

The sensitivity analyses for any AE had similar results to the primary analyses. Varying the censoring date from 0 to 90 days produced similar risks (0 days: HR, 1.18 [CI, 1.11 to 1.25]; 90 days: HR, 1.17 [CI, 1.10 to 1.25]). Furthermore, broadening the outcome to include possible events did not change the risk (HR, 1.17 [CI, 1.10 to 1.24]); neither did including MedDRA-coded events (**Table 2**).

Finally, we examined AEs during the prerandomization period (**Appendix Table 2**, available at Annals.org) and baseline correlates of participants who were not assigned to a group. The types of AEs observed during the active run-in period of 5 to 8 weeks were similar to those observed during the postrandomization period. Many of the renal or hematologic events noted in **Appendix Table 2** were abnormal laboratory values.

## DISCUSSION

Low-dose MTX is the most commonly used drug for systemic rheumatic diseases worldwide and is the recommended first-line agent for rheumatoid arthritis. Yet, despite extensive clinical use for more than 30 years, few data on AE rates derive from randomized, double-blind, placebo-controlled trials, where both causality and magnitude of risk can be inferred. Here, in a contemporary clinical trial that included recommended use of folic acid to reduce drug-associated toxicities, we observed statistically significant increases in risk for any adjudicated AE of interest, as well as for infectious, pulmonary, gastrointestinal, and hematologic AEs. We also observed an increase in skin cancer and an unanticipated reduction in renal AEs, mostly related to differences in final eGFR.

Existing data for LD-MTX toxicity derive almost exclusively from case reports, case series, and observational studies, which have been both inconclusive and contradictory. For example, although at least 3 prior studies found significant increases in infection risk among patients with rheumatoid arthritis using LD-MTX compared with no immunosuppressive agents (22, 23, 40), other studies have found no increase in risk for pneumonia and objectively confirmed infections (41, 42). We believe that the current data provide what are perhaps the first objective measurements of true toxicity associated with use of LD-MTX—risks that need to be balanced with the clear clinical benefits of this drug's use in the setting of rheumatoid arthritis or psoriasis.

***Table 5.*** Frequency and Relative Risks Comparing Infection and Pulmonary AEs for Methotrexate Versus Placebo During the Randomized Phase of CIRT*

| AE | Low-Dose Methotrexate ($n$ = 2391) | | | Placebo ($n$ = 2395) | | | Risk Difference (95% CI)‡ | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | Events, $n$ (%)† | Rate per 100 Person-Years (95% CI) | 3-y Cumulative Incidence (95% CI), % | | |
| **Infection** | | | | | | | | |
| Any | 531 (22.2) | 13.6 (12.4 to 14.8) | 0.31 (0.28 to 0.34) | 466 (19.5) | 11.8 (10.8 to 12.9) | 0.27 (0.25 to 0.30) | 0.04 (0.00 to 0.07) | 1.15 (1.01 to 1.30) |
| Mild | 340 (14.2) | 8.2 (7.4 to 9.1) | 0.20 (0.18 to 0.23) | 282 (11.8) | 6.8 (6.0 to 7.6) | 0.16 (0.14 to 0.18) | 0.04 (0.01 to 0.07) | 1.21 (1.03 to 1.42) |
| Moderate | 241 (10.1) | 5.6 (4.9 to 6.3) | 0.14 (0.12 to 0.16) | 219 (9.1) | 5.1 (4.4 to 5.7) | 0.13 (0.12 to 0.16) | 0.01 (−0.02 to 0.03) | 1.10 (0.91 to 1.32) |
| Severe | 51 (2.1) | 1.1 (0.8 to 1.4) | 0.03 (0.02 to 0.04) | 50 (2.1) | 1.1 (0.8 to 1.4) | 0.03 (0.03 to 0.05) | 0.00 (−0.02 to 0.01) | 1.02 (0.69 to 1.50) |
| By type | | | | | | | | |
| Upper respiratory infection/flu syndrome | 125 (5.2) | 2.8 (2.3 to 3.3) | 0.08 (0.07 to 0.10) | 105 (4.4) | 2.4 (1.9 to 2.8) | 0.06 (0.05 to 0.08) | 0.01 (0.00 to 0.03) | 1.19 (0.92 to 1.54) |
| Skin and soft tissue | 129 (5.4) | 2.9 (2.4 to 3.4) | 0.08 (0.07 to 0.09) | 125 (5.2) | 2.8 (2.3 to 3.3) | 0.08 (0.07 to 0.10) | 0.00 (−0.02 to 0.02) | 1.03 (0.80 to 1.31) |
| Pneumonia | 67 (2.8) | 1.5 (1.1 to 1.8) | 0.04 (0.03 to 0.06) | 52 (2.2) | 1.1 (0.8 to 1.4) | 0.03 (0.02 to 0.04) | 0.01 (0.00 to 0.02) | 1.28 (0.89 to 1.83) |
| Eye, ear, nose, throat, and dental | 182 (7.6) | 4.1 (3.5 to 4.7) | 0.11 (0.09 to 0.13) | 149 (6.2) | 3.4 (2.9 to 4.0) | 0.08 (0.07 to 0.10) | 0.03 (0.01 to 0.05) | 1.21 (0.98 to 1.51) |
| Genitourinary | 111 (4.6) | 2.5 (2.0 to 2.9) | 0.06 (0.05 to 0.08) | 86 (3.6) | 1.9 (1.5 to 2.3) | 0.05 (0.04 to 0.07) | 0.01 (−0.01 to 0.03) | 1.30 (0.98 to 1.72) |
| Gastrointestinal | 37 (1.5) | 0.8 (0.5 to 1.1) | 0.02 (0.02 to 0.03) | 35 (1.5) | 0.8 (0.5 to 1.0) | 0.02 (0.02 to 0.03) | 0.00 (−0.01 to 0.01) | 1.05 (0.66 to 1.67) |
| Shingles | 23 (1.0) | 0.5 (0.3 to 0.7) | 0.01 (0.01 to 0.02) | 17 (0.7) | 0.4 (0.2 to 0.5) | 0.01 (0.01 to 0.02) | 0.00 (0.00 to 0.01) | 1.34 (0.72 to 2.51) |
| Bone and joint | 21 (0.9) | 0.5 (0.3 to 0.6) | 0.01 (0.01 to 0.02) | 11 (0.5) | 0.2 (0.1 to 0.4) | 0.01 (0.01 to 0.02) | 0.00 (0.00 to 0.01) | 1.91 (0.92 to 3.96) |
| Yeast | 6 (0.3) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 9 (0.4) | 0.2 (0.1 to 0.3) | 0.01 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.66 (0.24 to 1.83) |
| Sepsis | 12 (0.5) | 0.3 (0.1 to 0.4) | 0.01 (0.00 to 0.01) | 14 (0.6) | 0.3 (0.1 to 0.5) | 0.01 (0.00 to 0.01) | 0.00 (−0.01 to 0.00) | 0.85 (0.39 to 1.82) |
| Not otherwise specified | 22 (0.9) | 0.5 (0.3 to 0.7) | 0.01 (0.01 to 0.03) | 22 (0.9) | 0.5 (0.3 to 0.7) | 0.01 (0.01 to 0.02) | 0.00 (−0.01 to 0.01) | 0.99 (0.55 to 1.79) |
| **Pulmonary events** | | | | | | | | |
| Any | 137 (5.7) | 3.1 (2.6 to 3.6) | 0.08 (0.07 to 0.10) | 135 (5.6) | 3.1 (2.5 to 3.6) | 0.06 (0.05 to 0.07) | 0.03 (0.01 to 0.04) | 1.42 (1.14 to 1.77) |
| Mild | 77 (3.2) | 1.7 (1.3 to 2.1) | 0.05 (0.04 to 0.06) | 66 (2.8) | 1.5 (1.1 to 1.8) | 0.03 (0.02 to 0.05) | 0.01 (0.00 to 0.03) | 1.40 (1.02 to 1.93) |
| Moderate | 50 (2.1) | 1.1 (0.8 to 1.4) | 0.03 (0.02 to 0.04) | 61 (2.5) | 1.3 (1.0 to 1.7) | 0.02 (0.01 to 0.03) | 0.01 (0.00 to 0.02) | 1.41 (1.02 to 1.96) |
| Severe | 13 (0.5) | 0.3 (0.1 to 0.4) | 0.01 (0.00 to 0.02) | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.00 (0.00 to 0.00) | 0.01 (0.00 to 0.01) | 2.99 (1.34 to 6.65) |
| By type | | | | | | | | |
| Bronchitis | 116 (4.9) | 2.6 (2.1 to 3.1) | 0.07 (0.06 to 0.08) | 73 (3.0) | 1.6 (1.3 to 2.0) | 0.04 (0.03 to 0.06) | 0.02 (0.01 to 0.04) | 1.60 (1.19 to 2.14) |
| Cough | 4 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 5 (0.2) | 0.1 (0.0 to 0.2) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 0.80 (0.21 to 2.96) |
| Shortness of breath | 11 (0.5) | 0.2 (0.1 to 0.4) | 0.04 (0.03 to 0.06) | 8 (0.3) | 0.2 (0.1 to 0.3) | 0.03 (0.02 to 0.04) | 0.01 (0.00 to 0.02) | 1.36 (0.55 to 3.38) |
| COPD/asthma flare | 3 (0.1) | 0.1 (0.0 to 0.1) | 0.01 (0.00 to 0.01) | 6 (0.3) | 0.1 (0.0 to 0.2) | 0.01 (0.00 to 0.02) | 0.00 (−0.01 to 0.00) | 0.50 (0.13 to 1.99) |
| Pneumonitis | 7 (0.3) | 0.2 (0.0 to 0.3) | 0.00 (0.00 to 0.01) | 1 (0.0) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.01) | 0.00 (0.00 to 0.00) | 6.94 (0.85 to 56.0) |
| Not otherwise specified | 1 (0.0) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.01) | 2 (0.1) | 0.0 (0.0 to 0.1) | 0.00 (0.00 to 0.00) | 0.00 (0.00 to 0.01) | 0.48 (0.04 to 5.37) |

AE = adverse event; CIRT = Cardiovascular Inflammation Reduction Trial; COPD = chronic obstructive pulmonary disease.
* Based on the modified intention-to-treat analyses (see text for details).
† Includes first events of a given type; percentages refer to the number of participants with a given AE divided by all participants in the respective treatment group. The first mild, moderate, and severe event, as well as the first of each type of AE, were included.
‡ Based on the 3-y cumulative incidence percentage of risk.

For many of the toxicities noted here, prescribers of LD-MTX should be aware of specific clinical situations and predictors of risk; some of these predictors have been described (22, 25), and others will be examined in future analyses.

The reduction in risk for renal AEs was unanticipated and small. The high-dose MTX used for oncology patients is known to be associated with renal toxicity (53). Methotrexate is renally cleared, and thus kidney function needs to be monitored during treatment, even with LD-MTX. Although review articles describe renal toxicity of LD-MTX in rheumatoid arthritis (54), it is difficult to find cases of renal toxicity during use of LD-MTX when other drugs (such as nonsteroidal anti-inflammatory drugs or cyclosporine) or other causes (such as renal amyloid) could not have contributed. Almost no data exist on a potential renal protective effect of LD-MTX, except in rodents with collagen-induced arthritis (55). However, a robust body of literature suggests that inflammation accelerates chronic kidney disease (56) and diabetic kidney disease (57). It is possible that LD-MTX improved eGFR through its effect on inflammation.

In addition to our ability to conduct the current analyses in the setting of a randomized, placebo-controlled trial, 2 other aspects of the methods should be highlighted. First, active run-in facilitates improved adherence after randomization because participants who do not tolerate the study drug or adhere to follow-up procedures can be identified and excluded. However, it would also reduce AE rates after randomization.

Second, we prespecified AEs of interest and prospectively adjudicated them using structured procedures with clinical criteria that were based on prior work or developed for this study (47–50). Trials designed to examine potential benefits do not usually examine and adjudicate AEs with this level of rigor. This step allows us to better characterize the nature and severity of the AEs. In addition, the adjudication procedures were blinded to treatment assignment. Severity of the AEs was based on clinical context (**Appendix Table 3**, available at Annals.org) and not on the typical MedDRA criteria for a "serious AE," defined simply as life-threatening or causing hospitalization.

The results of the current study need to be viewed in light of potential limitations. CIRT was not done in patients with systemic rheumatic disease. Absolute risks for AEs may differ between the CIRT population and typical patients with systemic rheumatic disease, who have higher levels of systemic inflammation and often use concomitant immunosuppressive agents. Such patients may metabolize LD-MTX differently for various reasons, including differences in gut microbiota (58). However, the relative risks probably do not differ, although this is not testable in our study cohort. Staff elicited AEs systemically at routine study visits every 4 to 12 weeks, but patients may have had AEs between visits and not reported them. This underreporting would affect both treatment groups similarly and thus is unlikely to introduce systematic bias. It is also possible that intensive monitoring of patients for AEs resulted in increased reporting. All patients in CIRT had tolerated LD-MTX during an active run-in period. The median follow-up of nearly 2 years was much longer than that in most LD-MTX trials, but it may still be too short to observe some AEs that require long-term exposure. Finally, patients in the placebo group (and those receiving LD-MTX) took folate 6 days each week; folate may have affected rates of AEs in both groups.

In conclusion, we found that LD-MTX users had increased risk for any AE, as well as for hematologic, skin cancer, gastrointestinal, liver, infectious, and pulmonary AEs. The risk for AEs that we observed in the LD-MTX group, such as cirrhosis and pneumonitis, generally agrees with prior reports (19, 40). The fact that median dosages of LD-MTX and placebo were very similar suggests relatively good tolerability of LD-MTX when given with folate. Moreover, strong data indicate that LD-MTX is efficacious for many patients with rheumatoid arthritis, and it is recommended as first-line treatment. The data presented here provide an important source of new evidence to improve the monitoring guidelines and safe prescribing of LD-MTX.

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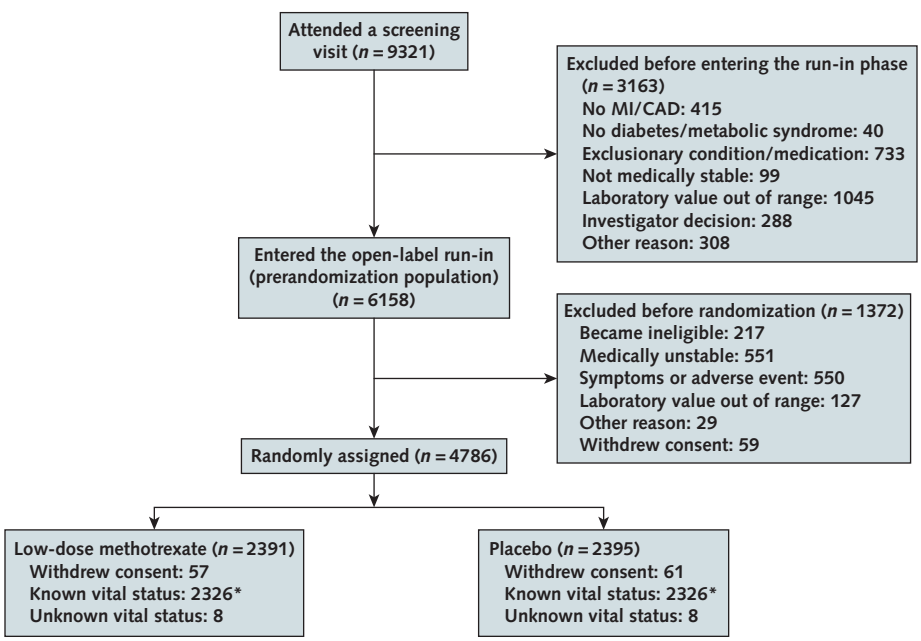
***Appendix Figure.*** Study flow diagram.




CAD = coronary artery disease; MI = myocardial infarction. (Reproduced from reference 46 with permission of the *New England Journal of Medicine*.)

* Within 3 mo of trial completion.

***Appendix Table 1.*** Selection Criteria for CIRT

**Inclusion criteria**

- Age ≥18 y
- Myocardial infarction in the past
- Multivessel coronary artery disease by angiography
- Type 2 diabetes and/or metabolic syndrome
- Completed all planned revascularization procedures
- Medically stable for 60 d from index myocardial infarction, surgical procedure, or other significant illness (including newly diagnosed diabetes)
- Participants were required to meet the following cell count requirements at screening: hematocrit ≥0.32, leukocyte count ≥3.50 × $10^9$ cells/L, and platelet count ≥75 × $10^9$ cells/L

**Exclusion criteria**

- Chronic liver disease
- Chronic inflammatory condition, such as lupus or rheumatoid arthritis, ulcerative colitis, or Crohn disease
- Chronic infectious disease
- Interstitial lung disease or pulmonary fibrosis
- Myeloproliferative disease in past 5 y
- HIV-positive
- Requirement for, or intolerance to, methotrexate or folate
- History of non–basal cell cancer or treatment of lymphoproliferative disease in past 5 y
- Requirement for use of drugs that alter folate metabolism
- History of alcohol abuse or unwillingness to limit consumption to <4 drinks/wk
- Women of childbearing potential (even if using oral contraceptive agents) or intending to breastfeed
- Men who plan to father children during the study period or are unwilling to use contraception
- Life expectancy <3 y or unlikely to adhere in judgment of investigator
- Long-term use of oral or intravenous steroid therapy or other immunosuppressive or biologic response modifiers
- History of hepatitis B or C
- Chronic pericardial effusion, pleural effusion, or ascites
- New York Heart Association class IV heart failure

CIRT = Cardiovascular Inflammation Reduction Trial.

***Appendix Table 2.*** Prerandomization AE Rate Among 6158 Participants During the Active Run-in Phase Using Low-Dose Methotrexate*

| AE | Events, *n (%)* |
|---|---|
| **All adjudicated and laboratory AEs** | 3102 (50.4) |
| Mild | 2898 (47.1) |
| Moderate | 238 (3.9) |
| Severe | 32 (0.5) |
| **By subtype** | |
| Infection | 77 (1.3) |
| Cancer | 13 (0.21) |
| Hematologic | 1321 (21.5) |
| Bleeding | 40 (0.7) |
| Pulmonary | 20 (0.3) |
| Liver | 341 (5.5) |
| Gastrointestinal | 138 (2.2) |
| Neuropsychiatric | 10 (0.2) |
| Mucocutaneous | 76 (1.2) |
| Musculoskeletal | 6 (0.1) |
| Renal | 1118 (18.2) |
| **All coded AEs** | 2733 (44.4) |
| **Only MedDRA AEs** | 967 (15.7) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
* Prerandomization period was 5–8 wk in duration.

*Appendix Table 3.* AEs of Interest With Severity Definitions

| Type of AE and Level of Severity | Severity Definition |
|---|---|
| **Infectious** | |
| Mild | Oral antibiotics or no treatment/without hospitalization |
| Moderate | IV antibiotics required and/or hospitalization for infection, or viral infection with probable etiology |
| Severe | Intensive care unit or operating room for debridement required |
| **Cancer** | No severity ratings; all considered severe except basal and squamous cell skin cancer |
| **Hematologic** | |
| Mild | Hemoglobin level, >LLN to 100 g/L; platelet count, >LLN to 75 × $10^9$ cells/L; leukocyte count, 3.000–3.999 × $10^9$ cells/L |
| Moderate | Hemoglobin level, 80–100 g/L; platelet count, 50–75 × $10^9$ cells/L; leukocyte count, 2.000–2.999 × $10^9$ cells/L |
| Severe | Hemoglobin level <80 g/L; platelet count <50 × $10^9$ cells/L; leukocyte count <2.000 × $10^9$ cells/L |
| **Pulmonary** | |
| Mild | Symptoms without imaging changes |
| Moderate | Symptoms + imaging changes and/or PFT changes |
| Severe | Imaging changes and/or PFT changes with requirement of supplemental oxygen |
| **Hepatic** | |
| Mild | LFTs 1–2× ULN and/or no more than fatty liver by imaging |
| Moderate | LFTs >2× ULN; no evidence of cirrhosis by imaging or biopsy |
| Severe | LFTs >2× ULN; evidence of cirrhosis by imaging or biopsy |
| **Bleeding*** | |
| Mild | Type 1 BARC |
| Moderate | Types 2 and 3 BARC |
| Severe | Types 4 and 5 BARC |
| **Kidney injury** | |
| Mild | Any elevation from baseline to <2× baseline serum creatinine |
| Moderate | Any elevation from baseline −1.9× baseline serum creatinine |
| Severe | ≥3× baseline serum creatinine |
| **Gastrointestinal** | |
| Mild | Symptoms reported, but no treatment for gastrointestinal symptoms given |
| Moderate | Symptoms reported and any treatment given, but not IV and not hospitalized for gastrointestinal symptoms |
| Severe | Symptoms reported and either hospitalized or IV treatments given |
| **Mucocutaneous** | |
| Mild | No treatments given and not hospitalized |
| Moderate | Treatments given and not hospitalized |
| Severe | Hospitalized for symptoms |
| **Musculoskeletal/neurologic** | |
| Mild | No hospitalization and no treatments |
| Moderate | Treatments given |
| Severe | Hospitalized for symptoms |

AE = adverse event; BARC = Bleeding Academic Research Consortium; IV = intravenous; LFT = liver function test; LLN = lower limit of normal; PFT = pulmonary function test; ULN = upper limit of normal.
* Based on BARC categories.