VIEWPOINT

Is Myocardial Infarction Overdiagnosed?

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More than 750 000 individuals receive a diagnosis of myocardial infarction (MI) each year in the United States. This large number represents a small numerator compared with the massive denominator of the total number of individuals evaluated for the diagnosis. An enormous number of individuals are evaluated for MI because its underdiagnosis has become a major concern for clinicians. A now-classic study from 2 decades ago showed that 2% of individuals with MI were mistakenly discharged from the emergency department (ED) and such misdiagnosis of MI was associated with an increased risk of all-cause mortality.[1] Since then, failure to diagnose MI has been a major cause of malpractice litigation in the United States. In response, the diagnosis of MI is now commonly sought among individuals presenting to the ED even when symptoms or signs for the diagnosis are subtle, atypical, or completely absent. Inevitably, this practice leads to incorrect identification of MI in persons without the diagnosis. In this Viewpoint, we argue that misdiagnosis of MI is now most often due to the incorrect identification of the diagnosis rather than to its being missed.

Although reducing missed diagnosis of MI has been an imperative endeavor, incorrect diagnosis of MI is not benign: individuals with suspected MI are routinely prescribed medical treatments that may expose them to adverse effects. Patients incorrectly assigned a diagnosis of MI are often subjected to further testing, including high-cost imaging and potentially risky invasive procedures. Other forms of health care use are also inflated by misdiagnosis of MI, including needless consultations, prolonged ED stays, and unnecessary hospitalizations. Beyond these concerning issues, 1 in 5 of all individuals with an MI diagnosis experiences depression, one-third face financial hardship with medication costs, and one-tenth experience an adverse change in their employment status.[2] The diagnosis may also affect an individual's eligibility for, or cost of, life insurance. At a population level, overdiagnosis of MI may also have distorting effects; misdiagnosis of MI may lead to changing payment for inpatient hospitalizations or inappropriate inclusion of data in influential quality programs linked to financial incentives.

> Overdiagnosis as opposed to underdiagnosis may now be the dominant form of MI misdiagnosis.

Overdiagnosis of MI: The Scope of the Problem

Emerging evidence suggests that incorrect overdiagnosis of MI is more common than its underdiagnosis. An example is reflected in results from clinical trials; several trials with central event adjudication committees have reported 15% to 20% fewer type 1 MI events than the site investigators reported when applying the recommendations of the Universal Definition of Myocardial Infarction working group.[3,4] These data are not unique to clinical trial cohorts. In a multicenter population with clinically diagnosed MI, 9% of events were refuted and reclassified as myocardial injury when adjudicated by an expert consensus.[5] Studies incorporating cardiac magnetic resonance imaging also point to overdiagnosis. For instance, in the Women's Heart Attack Research Program, only half of patients with clinically diagnosed MI had an infarction pattern on their cardiac magnetic resonance imaging result, and alternative diagnoses such as myocarditis were identified for one-fifth of participants.[6] However, in contrast to studies focused on the relatively small number of patients with missed MI who are discharged from the ED, few data exist regarding the frequency and consequences of incorrect overdiagnosis of MI.

Factors That May Contribute to Overdiagnosis of MI

The Universal Definition of Myocardial Infarction working group defines the diagnosis according to symptoms and signs of coronary ischemia together with evidence of myocardial injury as reflected in an increase in cardiac troponin level, a decrease in the level, or both. Although an abnormal troponin level is necessary to make a diagnosis of MI, that result alone is not sufficient to do so. Compounding this problem, liberal troponin testing has become commonplace, particularly in the United States. In one study, a quarter of individuals presenting to the ED underwent a troponin test, with fewer than half complaining of chest pain.[7] Low pretest probability reduces the posttest validity of any result, an issue that is further complicated by analytic aspects of the increasingly sensitive assays for troponin that are now widely available. First, these assays are often affected by noncoronary comorbid conditions. Because patients undergoing ED evaluations tend to be older and with more comorbid conditions, abnormalities in troponin level in the absence of MI are common; among unselected ED cohorts, approximately 1 in 7 patients will have an elevated concentration.[8] Second, although troponin level represents the most specific biomarker for diagnosing MI, mechanisms beyond ischemic necrosis such as apoptosis and exocytosis (which can occur in noncoronary disease states) are implicated in troponin elevation. Therefore, abnormal troponin concentrations, even when dynamic, may not necessarily reflect myocardial ischemic necrosis. Third, although the 99th percentile upper reference limit for high-sensitivity troponin (derived from apparently healthy adult cohorts) is central to an MI diagnosis, this value is typically derived

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from cohorts of young or middle-aged adults (<59 years); if identified from older adults (≥60 years), the 99th percentile for that age category would be 1.5- to 2.0-fold higher.[9] Because most MIs occur in older individuals, these data raise the possibility of overdiagnosis of MI in older adults if troponin thresholds derived from generally younger, healthier individuals are used. Fourth, although the 99th percentile value represents an accepted criterion for diagnosis of myocardial injury, a complete lack of understanding exists about optimal values to identify an abnormal troponin level increase or decrease associated with MI. For all these reasons, in the setting of frequent testing with low pretest probability and analytic vulnerabilities of the troponin assays that are so heavily depended on for MI diagnosis, the positive predictive value of a troponin test result for MI in the United States is significantly lower (≈16%) than in the United Kingdom (≈60%).[8] This lower positive predictive value of troponin testing result for MI in studies in the United States strongly supports that overtesting and misdiagnosis are occurring.[8]

Strategies to Reduce MI Overdiagnosis

There are several opportunities to reduce the risk of MI overdiagnosis. Although missing an MI should never occur, tort reform laws capping noneconomic damage payments in malpractice cases are needed to stem the practice of defensive medicine; such laws may reduce health care expenditures without loss of care quality.[10] Beyond this step, pretest probability before troponin testing must be considered; such testing should be applied only to individuals with suspected acute coronary syndrome and not applied relatively unselectively to individuals presenting to the ED. Machine learning models have the potential to improve accuracy of MI diagnosis beyond current MI diagnostic pathways. Such models may incorporate fixed and dynamic variables to more accurately predict MI diagnosis. Implementation of age-specific 99th percentiles should be considered to reduce overdiagnosis of abnormal troponin concentrations in older adults. Furthermore, better adherence to the Universal Definition of Myocardial Infarction guidelines is critically important, with attention paid to the nonbiomarker aspects of the definition; depending on troponin level alone to render a diagnosis of MI is fraught with risk for misdiagnosis. Beyond troponin, continued development of biomarkers specific for the detection of myocardial necrosis as opposed to myocardial injury is needed. Last, prudent use of cardiac imaging, particularly for ambiguous cases, may provide further opportunity to improve the accuracy of MI diagnosis.

Conclusions

Overdiagnosis as opposed to underdiagnosis may now be the dominant form of MI misdiagnosis. Overdiagnosis of MI is not benign and exposes patients to risks of unnecessary testing, treatments, and costs and may distort both hospital payments and the intended effects of health policies. Further studies are needed to better understand the frequency and implications of overdiagnosis of MI while identifying, evaluating, and implementing strategies to ensure appropriate and accurate evaluations for the diagnosis.

ARTICLE INFORMATION

Published Online: April 24, 2024. doi:10.1001/jama.2024.5235

Conflict of Interest Disclosures: Dr McCarthy is supported by a National Heart, Lung, and Blood Institute Career Development Award (K23HL167659) and reported receiving consulting fees and honoraria from Roche Diagnostics and Abbott Laboratories outside the submitted work. Dr Wasfy is chair of the New England Comparative Effectiveness Public Affairs Council and reported receiving grant support from the National Institutes of Health (R01AG062282) and consulting fees from Pfizer outside the submitted work. Dr Januzzi is a trustee of the American College of Cardiology, a board member of Imbria Pharmaceuticals, and a director at Jana Care; reported receiving research support from Abbott, Applied Therapeutics, Bayer, BMS, HeartFlow, Innolife, Medtronic, and Roche Diagnostics; reported receiving consulting income from Abbott, AstraZeneca, Bayer, Beckman, Boehringer Ingelheim, Cytokinetics, Janssen, Merck, Novartis, Prevencio, QuidelOrtho, and Roche Diagnostics; and participates in clinical end point committees and data and safety monitoring boards for Abbott, AbbVie, Axon, Bayer, CVRx, Medtronic, Pfizer, Roche Diagnostics, and Takeda. No other disclosures were reported.

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