stitions. However, no association was found between hospital review of PCI appropriateness with procedural appropriateness, use of guideline-recommended care, or clinical outcomes.

The AUC for coronary revascularization provide patients, health care professionals, payers, and policymakers with an opportunity to critically examine clinical practice patterns and decision making about patient selection for PCI with the hope of reducing rates of rarely appropriate PCIs while improving patient outcomes. Our finding that a quarter of hospitals do not conduct reviews of AUC suggests that many hospitals have not prioritized improving their performance on AUC. Whether the continued incorporation of PCI appropriateness into public reporting and pay-for-performance programs further incentivizes institutional efforts to improve patient selection for PCI deserves further study.

The presence of regular review alone may be insufficient to improve procedural appropriateness. We observed that differences in institutional PCI appropriateness review were not associated with hospitals’ rates of rarely appropriate PCI. This finding may reflect the fact that the frequency of appropriateness review is a limited measure of the intensity of an institution’s response to the AUC and the reality that review of AUC must be coupled with other enabling structures to be effective. Our survey instrument did not systematically collect additional details of review, including the nature of appropriateness review (prospective or retrospective) or the specific format of the review process.

Consistent with prior studies, there was a modest association between procedural appropriateness and clinical outcomes and a similarly modest correlation between nonacute PCI volume and procedural appropriateness. Of note, hospitals with a higher volume of nonacute PCI had a lower proportion of rarely appropriate PCI across all review frequencies. Whether this finding is related to the presence of better communication, leadership, and oversight at higher-volume PCI centers is unclear. There is a pressing need to identify effective strategies that can be used to support institutional improvement of PCI appropriateness.

Nihar R. Desai, MD, MPH
Craig S. Parzynski, MS
Harlan M. Krumholz, MD, SM
Karl E. Minges, MPH
John C. Messenger, MD
Brahmajee K. Nallamothu, MD, MPH
Jeptha P. Curtis, MD

Author Affiliations: Section of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine, New Haven, Connecticut (Desai, Krumholz, Curtis); Center for Outcomes Research and Evaluation, Yale–New Haven Health Services Corporation, New Haven, Connecticut (Desai, Parzynski, Krumholz, Minges, Curtis); Division of Cardiology, University of Colorado School of Medicine, Aurora (Messenger); Division of Cardiovascular Diseases, University of Michigan, Ann Arbor (Nallamothu); Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Michigan (Nallamothu).

Corresponding Author: Jeptha P. Curtis, MD, Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, PO Box 208017, New Haven, CT 06520-8017 (jeptha.curtis@yale.edu).

Published Online: November 9, 2015. doi:10.1001/jamainternmed.2015.6217.

Author Contributions: Drs Desai and Curtis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Desai, Curtis.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Desai, Parzynski.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Parzynski.

Obtained funding: Desai, Curtis.

Administrative, technical, or material support: Desai, Minges, Messenger.

Conflict of Interest Disclosures: Drs Desai and Krumholz reported receiving a research agreement from Johnson & Johnson, through Yale University, to develop methods of clinical trial data sharing. Drs Desai, Krumholz, and Curtis reported receiving funding from the Centers for Medicare & Medicaid Services to develop and maintain performance measures that are used for public reporting. Dr Krumholz reported receiving research support from Medtronic, through Yale University, to develop methods of clinical trial data sharing and of a grant from the US Food and Drug Administration to develop methods for postmarket surveillance of medical devices. Dr Krumholz reported chairing a cardiac scientific advisory board for UnitedHealth. Dr Curtis reported holding equity interest in Medtronic. No other disclosures were reported.

Funding/Support: This study was supported by the National Cardiovascular Data Registry (Mr Parzynski and Dr Curtis), grant K12 HS023000-01 from the Agency for Healthcare Research and Quality (Dr Desai), and grant U01 HL10570-05 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute (Drs Krumholz and Curtis and Mr Minges).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Information: The National Cardiovascular Data Registry’s CathPCI Registry is an initiative of the American College of Cardiology Foundation and the Society for Cardiovascular Angiography and Interventions.


Risk of Demyelinating Diseases in the Central Nervous System in Patients With Inflammatory Bowel Disease Treated With Tumor Necrosis Factor Inhibitors

An association between usage of tumor necrosis factor inhibitors (anti-TNF) in patients with inflammatory bowel disease (IBD) and other immune-mediated diseases and demyelinating diseases in the central nervous system has been sug-
gested by case reports. However, it remains uncertain whether these cases are directly related to anti-TNF therapy because there is evidence of an underlying association between demyelinating disease and IBD. In a nationwide population-based cohort, we compared rates of central demyelinating diseases among patients with IBD exposed and unexposed to anti-TNF.

**Methods** | The general study design and data sources used have been described in detail elsewhere. Briefly, using the Danish Civil Registration System, we identified a source population of 4 million people living in Denmark from January 1, 1999, to December 31, 2012. Unique personal identifiers permitted linkage to data from health registries on IBD diagnoses, anti-TNF exposure, and outcomes. After the date of first anti-TNF dose, the patient was categorized as ever exposed. The outcome was defined as a diagnosis of a central demyelinating disease, including multiple sclerosis, optic neuritis, transverse myelitis, and other central demyelinating diseases. Patients with a history of central demyelinating disease and those with use of anti-TNF prior to 1999 or prior to IBD diagnosis were excluded. The study was approved by the Danish Data Protection Agency. Ethics approval is not required for registry-based research in Denmark.

Patients exposed to anti-TNF and those unexposed were matched in a ratio of up to 1:4 on sex, age (5-year interval), and disease duration (<1, 1-4, 5-9, 10-19, and ≥20 years). The cumulative incidences of central demyelinating disease were analyzed using a competing risk model (Aalen-Johansen method). The hazard ratio (HR) was estimated using Cox regression with time since anti-TNF treatment initiation as underlying timescale. Patients were followed from cohort entry (date of first anti-TNF dose for the exposed patients, which was also set as entry date for the corresponding unexposed matches) until first diagnosis of a central demyelinating disease, 5 years of follow-up, emigration, death, or the end of the study (December 31, 2012), whichever event occurred first. No violation of the proportional hazards model assumption was detected. Analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc).

**Results** | From the source population, 54,843 patients with IBD were identified. Among these, 4,504 were exposed to anti-TNF and matched to 16,429 unexposed patients, yielding a study cohort of 20,933 patients. Anti-TNF–exposed patients in the matched cohort had a mean (SD) age of 39.4 (14.7) years, 56% were female, and the mean disease duration was 4.0 years (interquartile range [IQR], 1.1-9.0).

A total of 11 central demyelinating events were observed in exposed patients (2 cases of multiple sclerosis; 5, optic neuritis; 4, other central demyelinating diseases; corresponding to 7.5 events per 10 000 person-years [95% CI, 4.1-13.5]). In unexposed patients, there were 17 central demyelinating events (5 cases of multiple sclerosis; 6, optic neuritis; 1, transverse myelitis; 5, other central demyelinating diseases; resulting in 3.3 events per 10 000 person-years [95% CI, 2.1-5.4]).

The HR for central demyelinating disease comparing anti-TNF–exposed and unexposed patients was 2.19 (95% CI, 1.02-4.71) with an absolute risk difference of 3.9 per 10 000 person-years (95% CI, 0.1-12.2). The Figure presents cumulative incidences of demyelinating events.

To test for impact of control sampling (because the number of unexposed patients by far exceeded those exposed, our analysis might be sensitive to which patients were selected as controls), we ran the analysis 10,000 times with a new random selection of controls in each analysis. The median HR of the 10,000 analyses was 1.95 (IQR, 1.70-2.25), thus confirming that the observed 2-fold increased risk was not due to control selection.

**Discussion** | This population-based cohort study suggests a possible 2-fold increased relative risk but a low absolute risk of central demyelinating diseases associated with anti-TNF exposure in patients with IBD. While these preliminary find-

**Figure.** Cumulative Incidences of Central Demyelinating Diseases in Matched Anti–Tumor Necrosis Factor (TNF) Exposed and Unexposed Patients With Inflammatory Bowel Disease Through 5 Years of Follow-up
lings could be due to a chance or unmeasured confounding and need confirmation in other studies, they do represent the first analytical data of this potential association. If true, the observed association could either be attributed to the unmasking of a latent demyelinating disease6 or to the emergence of a de novo demyelinating disease.1

The rarity of demyelinating diseases limited the statistical power and capacity to adjust for or match on potential confounder variables. Thus, the estimates should be interpreted with caution because confounding cannot be excluded.

Nynne Nyboe Andersen, MD
Bjørn Pasternak, MD, PhD
Mikael Andersson, MSc
Nette Munk Nielsen, MD, PhD
Tine Jess, MD, DMSc

Author Affiliations: Department of Epidemiology Research, Statens Serum Institut, 2300 Copenhagen S, Denmark.

Corresponding Author: Nynne Nyboe Andersen, MD, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark (nyma@ssi.dk).


Author Contributions: Dr Nyboe Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Andersen.

Critical revision of the manuscript for important intellectual content: Pasternak, Andersson, Nielsen, Jess.

Statistical analysis: Nyboe Andersen, Andersson.

Obtained funding: Nyboe Andersen, Jess.

Study supervision: Pasternak, Nielsen, Jess.

Conflict of Interest Disclosures: Dr Nyboe Andersen has received funding for travel and speakers fee from MSD and speakers fee from Ferring. No other disclosures are reported.

Funding/Support: This study was supported by grants from the Lundbeck Foundation (grant No. R83-A7812), for Women in Science (by UNESCO and L’Oréal), the Beckett Foundation, and the Danish Colitis Crohn Association. Dr Pasternak is supported by the Danish Council for Independent Research (grant No. 4092-00155). Dr Jess holds a Female Research Leader grant (No. 09-066323) from the Danish Council for Independent Research.

Role of the Sponsor: The funding agencies had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.


HEALTH CARE REFORM
Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals

Most contemporary approvals of new cancer drugs are made on the basis of a surrogate end point, such as response rate or progression-free survival (PFS).1 When the approval is based on a surrogate end point, subsequent studies are advised and often obligated to clarify the drug’s effect on overall survival. One such drug is bevacizumab, which received accelerated approval on the basis of PFS for patients with metastatic breast cancer. Later findings revealed no improvement in overall survival and significant toxicity, which required a removal of marketing authorization.2

A 2009 Government Accountability Office report criticized the US Food and Drug Administration (FDA) for failing to enforce postmarketing study commitments for surrogate approvals. Among the more than 400 postmarketing studies requested, approximately 30% were pending, ongoing, delayed, or terminated years later, yet the FDA never exercised its authority to remove a product from the market.3 For these reasons, we sought to investigate how often cancer drugs are approved based on a surrogate end point, whether subsequent studies for these drugs are reported, and whether the drugs improve overall survival.

Methods | We examined all marketing approvals by the FDA from January 1, 2008, through December 31, 2012. We identified the pathway for approval (accelerated vs traditional) and the surrogate end point used, such as tumor response rate or PFS. This investigation of published reports was exempt from institutional review board approval.

For all drugs approved on the basis of a surrogate end point, we performed a systematic search of the published literature using Google Scholar as of August 22, 2015, and identified any subsequent reports of the drug’s effect on overall survival. We credited a drug for improving overall survival if that drug improved survival as the sole investigational agent in any combination or in any line of treatment (eg, if approved for second-line treatment of metastatic disease, but the drug improved survival in first-line treatment, we would credit the drug as improving survival). We identified whether crossover (from the control arm to the investigational agent) was used in the randomized clinical trial or via a postprotocol expansion study. We analyzed the study data from August 22 to September 1, 2015.

Results | We identified 54 approvals made during our search period, with 36 drugs (67%) approved on the basis of a surrogate end point. Figure 1 shows all surrogate approvals, the efficacy end point at the time of approval, and the regula-