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Author Contributions: Dr Pham-Kanter 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: Pham-Kanter. Acquisition of data: Pham-Kanter and Nair. Analysis and interpretation of data: Pham-Kanter, Alexander, and Nair. Drafting of the manuscript: Pham-Kanter, Alexander, and Nair. Critical revision of the manuscript for important intellectual content: Pham-Kanter, Alexander, and Nair. Statistical analysis: Pham-Kanter. Obtained funding: Pham-Kanter, Alexander, and Nair. Administrative, technical, and material support: Pham-Kanter and Nair. Study supervision: Pham-Kanter and Nair.

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Characteristics of “Complex” Patients With Type 2 Diabetes Mellitus According to Their Primary Care Physicians

Despite recent trends toward improved risk factor control, most patients with type 2 diabetes mellitus still do not achieve all evidence-based management goals,1 suggesting that new approaches are needed to further improve the quality of diabetes care. Patient complexity is a concept that is defined to describe the multiple factors that contribute to the challenges associated with clinical care.2 Because primary care physicians (PCPs) have a unique perspective on type 2 diabetes management, we hypothesized that greater insight into PCP-defined complexity among patients with type 2 diabetes could help inform strategies for improving diabetes primary care.

Methods. We conducted a cross-sectional analysis of PCP-defined patient complexity by asking 40 PCPs from the Massachusetts General Primary Care Practice-Based Research Network, Boston, to review randomly generated lists of 120 of their own patients and to designate which of these patients “in their view” they considered complex.3 Among the patients with type 2 diabetes, we examined the relative impact of diabetes-related vs other more general medical conditions on PCP-defined complexity. For each comorbid diagnosis that was significantly associated with complexity in univariate analysis, we constructed a separate logistic regression model and reported the relative odds of PCP-defined complexity after adjusting for age, sex, glycemic control, and patient clustering by PCP. The study was approved by the institutional review board of Massachusetts General Hospital, Boston.

Results. The PCPs reviewed 327 patients with type 2 diabetes (mean [SD] number of patients per PCP, 8.4 [5.1]; range, 2-25 patients per PCP) and designated 68.2% of these patients as complex. The PCP-defined complex patients with diabetes were 3 years older and more often female than noncomplex patients with diabetes but had similar race/
HbA1c levels were controlled for, the likelihood of being patients with diabetes. In separate models, after age, sex, and azepines (30.0% vs 13.5%; \(P = 0.03\)) therapy (36.3% vs 18.3%; \(P = 0.03\)) and benzodi- azepines (42.2% vs 25.0%; \(P = 0.03\)) were similar, and good low-density lipoprotein cholesterol control was achieved in both groups (mean [SD] HbA1c levels, 7.3% [1.5%] vs 6.9% [1.0%]; \(P = 0.003\)) than noncomplex patients, and a larger proportion had at least 1 HbA1c level greater than 9.0% (18.2% vs 8.1%; \(P = 0.03\)) or 10.0% (9.8% vs 1.0%; \(P = 0.003\)) in the previous year. While the proportion of patients who were receiving oral hypoglycemic medications was similar, complex patients were more often prescribed insulin (35.9% vs 19.2%; \(P = 0.003\)). The prevalence of hypertension diagnosis (88.8% complex vs 80.8% noncomplex; \(P = 0.06\)) and treatment (90.6% complex vs 84.6% noncomplex; \(P = 0.13\)) were similar in both groups. Similarly, the rates of lipid-lowering therapy prescription (76.7% vs 70.2%; \(P = 0.22\)) were similar, and good low-density lipoprotein cholesterol control was achieved in both groups (mean [SD] low-density lipoprotein level in previous year, 86.0 [28.5] mg/dL vs 89.4 [26.7] mg/dL [to convert to millimoles per liter, multiply by 0.0259]; \(P = 0.34\)).

Complex patients with diabetes had a significantly higher prevalence of comorbid conditions than noncom-plex patients with diabetes. Also, complex patients with diabetes were more likely to be prescribed narcotic analgesics (42.2% vs 25.0%; \(P = 0.03\)), selective serotonin reuptake inhibitors (33.6% vs 14.4%; \(P < 0.001\)), and benzodi-azepines (30.0% vs 13.5%; \(P = 0.001\)) and to require physical therapy (36.3% vs 18.3%; \(P < 0.001\)) than noncomplex patients with diabetes. In separate models, after age, sex, and HbA1c levels were controlled for, the likelihood of being designated as complex increased by 2- to 5-fold in the presence of atrial fibrillation (adjusted odds ratio [aOR], 5.0; 95% CI, 2.1-11.7), depression (aOR, 4.6; 95% CI, 1.7-12.2), heart failure (aOR, 3.3; 95% CI, 1.4-8.0), anxiety (aOR, 3.2; 95% CI, 1.3-4.4) osteoarthritis (aOR, 2.4; 95% CI, 1.3-4.4), or chronic obstructive pulmonary disease (aOR, 2.1; 95% CI, 1.1-4.0) (Figure).

Comment. The PCPs who reviewed a randomly selected list of their own patients designated just over two-thirds of their patients with type 2 diabetes mellitus as complex. Prevalence and management of the “core triad” of glycemia, blood pressure, and dyslipidemia did not appear to account for this complexity (with the exception of insulin use), which suggests that dyslipidemia and hypertension do not add substantially to the complexity of patients with type 2 diabetes. These findings indicate that—with the exception of facilitating insulin prescription—we may be reaching a “ceiling” on how much more benefit can be obtained in diabetes-specific quality improvement interventions.

In contrast, significant differences were seen in the prevalence of conditions such as atrial fibrillation, osteoarthritis, depression, and anxiety, conditions that may interfere with either the therapeutic relationship or the self-management activities that are necessary to achieve good diabetes control, suggesting that substantial advances in the quality of diabetes primary care may require focusing resources on these other comorbid conditions that complicate diabetes care.

The PCP-identified complex patients had significantly more outpatient clinical care contact during the previous year. Therefore, the patients in our study had ample opportunity to engage with the primary care system. Further improvements in diabetes management may thus require a greater emphasis on comprehensive, patient-centered rather than diabetes-specific interventions.

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Figure. Predictors of patient complexity adjusted for patient age, sex, and hemoglobin A1c (HbA1c) level. The adjusted odds ratios are derived from separated logistic regression models after adjustment for age, sex, mean HbA1c level in the previous year, and patient clustering by primary care physician. COPD indicates chronic obstructive pulmonary disease.
Brillation. Dabigatran was associated with lower risk of which enrolled more than 18,000 patients with atrial fibrillation of Long Term Anticoagulant Therapy (RE-LY) Trial, raised by the results of the landmark Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Trial, the results of the other 6 trials tend to the null hypothesis. Therefore, inclusion of RE-LY data in a meta-analysis designed to test an idea generated from the suspicion that MI risk could be higher in patients receiving dabigatran compared with warfarin was raised by the results of the landmark Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Trial, which enrolled more than 18,000 patients with atrial fibrillation. Dabigatran was associated with lower risk of the primary outcome (stroke or systemic embolism) and showed similar risk of the primary safety outcome (major hemorrhage). However, MI, one of several secondary outcomes, had an annual incidence of 0.74% for patients randomized to dabigatran therapy, 150 mg twice daily, and 0.53% for warfarin, corresponding to a 38% higher risk. On the basis of this finding, Uchino and Hernandez performed the meta-analysis, which apparently confirms the suspicion: a 33% higher risk of MI or ACS in patients taking dabigatran. However, we should recognize the possibility of this finding resulting from methodological artifact.

First, the finding from the RE-LY Trial was based on a secondary end point, which by nature has a greater predisposition to result from chance. Second, the trial that generated the hypothesis is by far the largest of the 7 studies in the meta-analysis. The RE-LY Trial has 18,000 patients, which is more than the samples of the other 6 studies put together. Thus, the relative risk estimate was highly influenced by the RE-LY Trial. Third, as opposed to the RE-LY Trial, the results of the other 6 trials tend to the null hypothesis. Therefore, inclusion of RE-LY data in a meta-analysis designed to test an idea generated from the same RE-LY Trial reduces the impact of the meta-analysis as a validation study. Based on this rationale, we performed a random-effect meta-analysis including all trials, except RE-LY. The summary odds ratio was 1.12 (95% CI, 0.66-1.9), thus much closer to the null hypothesis and statistically not significant.

In conclusion, the meta-analysis by Uchino and Hernandez was largely influenced by the RE-LY results and should not be viewed as a confirmation that MI risk is higher in patients receiving dabigatran.

**COMMENTS AND OPINIONS**

**Dabigatran and Myocardial Infarction: Meta-Illusion?**

We read with great interest the article by Uchino and Hernandez. By performing a meta-analysis of 7 randomized trials, they suggested that dabigatran therapy is associated with increased risk of myocardial infarction (MI) or acute coronary syndrome (ACS). Even though meta-analyses provide strong evidence for efficacy and safety, the role of chance should always be taken into account before definite conclusions.

The suspicion that MI risk could be higher in patients receiving dabigatran compared with warfarin was raised by the results of the landmark Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Trial, which enrolled more than 18,000 patients with atrial fibrillation. Dabigatran was associated with lower risk of the primary outcome (stroke or systemic embolism) and showed similar risk of the primary safety outcome (major hemorrhage). However, MI, one of several secondary outcomes, had an annual incidence of 0.74% for patients randomized to dabigatran therapy, 150 mg twice daily, and 0.53% for warfarin, corresponding to a 38% higher risk. On the basis of this finding, Uchino and Hernandez performed the meta-analysis, which apparently confirms the suspicion: a 33% higher risk of MI or ACS in patients taking dabigatran. However, we should recognize the possibility of this finding resulting from methodological artifact.

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In conclusion, the meta-analysis by Uchino and Hernandez was largely influenced by the RE-LY results and should not be viewed as a confirmation that MI risk is higher in patients receiving dabigatran.

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We appreciate the comments from Correia and Lopes. We acknowledge in the “Comment” section of our article that the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Trial had a large impact on our study, comprising 59% of the cohort and 74% of the events. In all of the 7 studies, myocardial infarction (MI) and acute coronary syndrome (ACS) were secondary safety outcomes, and limitations in interpreting secondary outcomes are true across the studies. Given the scarcity of MI and ACS events and the imbalance between trial arms, performing a Mantel-Haenszel fixed-effects model for meta-analysis is a better method than a random-effects model.

The risk derived from the 6 remaining studies is reported by Correia and Lopes to have an odds ratio of 1.12 (95% CI, 0.66-1.90). This does not exclude an increased risk. We found a consistently higher risk of MI and ACS with 12,000 more patients and 25% more events than the RE-LY Trial alone. We believe that our consistent results using different methods and models are not methodological artifacts.

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