CORRESPONDENCE

Association between Angiotensin Blockade and Incidence of Influenza in the United Kingdom

TO THE EDITOR: Some researchers have hypothesized that drugs that interfere with the renin–angiotensin–aldosterone system (RAAS), including angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), may increase susceptibility to coronaviruses. This hypothesis is based on the observation that coronaviruses engage ACE2 for cell entry[1] and that altered expression of *ACE2* is influenced by the use of ACE inhibitors and ARBs, an action that has been shown in animal models.[2] Influenza A (H7N9, H1N1, and H5N1) has been shown to use the ACE2 receptor to mediate lung damage, similar to that seen in severe acute respiratory syndrome (SARS).[3] Understanding the shared mechanism between SARS and influenza may help to address the question as to how ACE inhibitors and ARBs may modulate the manifestations of certain viral respiratory infections.

In this study, we used the linked electronic health care records of 5.6 million persons in the United Kingdom from the Clinical Practice Research Datalink (CPRD)[4] to investigate the incidence of influenza among adults (≥18 years of age) who had received a prescription for an ACE inhibitor from 1998 through 2016. Permission for the use of CPRD and Hospital Episode Statistics (HES) data for the research was provided by the CPRD independent scientific advisory committee. We defined exposure to an ACE inhibitor as a documented prescription during the study period. We performed additional analyses to assess the association between the incidence of influenza and the duration of use of an ACE inhibitor, which was defined as the sum of prescription days (categorized as none, <0.5 years, 0.5 to <1.5 years, 1.5 to <2.5 years, 2.5 to <3.5 years, 3.5 to <5.0 years, 5.0 to <7.5 years, 7.5 to <10.0 years, and ≥10.0 years). The same methods were used to assess the association between the use of ARBs and the incidence of influenza.

We identified 700,994 persons who had received a prescription for an ACE inhibitor and 230,028 who had received a prescription for an ARB. A total of 4,742,017 persons in the database had not received a prescription for an ACE inhibitor, an ARB, or the direct renin inhibitor aliskiren. Definitions of influenza were drawn from the Global Burden of Disease Study 2017,[5] including codes J09 through J11.8 of the *International Statistical Classification of Diseases, 10th Revision*. (Details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) Analyses were adjusted for age at baseline, sex, smoking history, presence of obesity, influenza vaccination, the presence of 12 coexisting conditions (diabetes, hypertension, stable angina, ischemic heart disease, atrial fibrillation, stroke, asthma, cancer, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, and dementia), and the time period of the influenza outbreak.

During a median 8.7 years of follow-up, persons who had received a prescription for an ACE inhibitor had a lower risk of influenza than those who had not (adjusted hazard ratio, 0.66; 95% confidence interval [CI], 0.62 to 0.70) (Fig. 1A and 1C). A curvilinear relationship was observed between the number of prescription days and incident influenza. As compared with no prescription days, the hazard ratio for incident influenza was 0.99 (95% CI, 0.91 to 1.07) for a duration of less than 0.5 years, 0.74 (95% CI, 0.65 to 0.85) for a duration of 2.5 to less than 3.5 years, and 0.52 (95% CI, 0.46 to 0.58) for a duration of 5.0 to less than 7.5 years. Analyses comparing the incidence of influenza and the use of ARBs showed results that were similar to the findings with ACE inhibitors (Fig. 1B and 1D).

Thus, the use of ACE inhibitors and ARBs was associated with either no effect on the incidence of influenza or a lower incidence, depending on the duration of use. These associations regarding

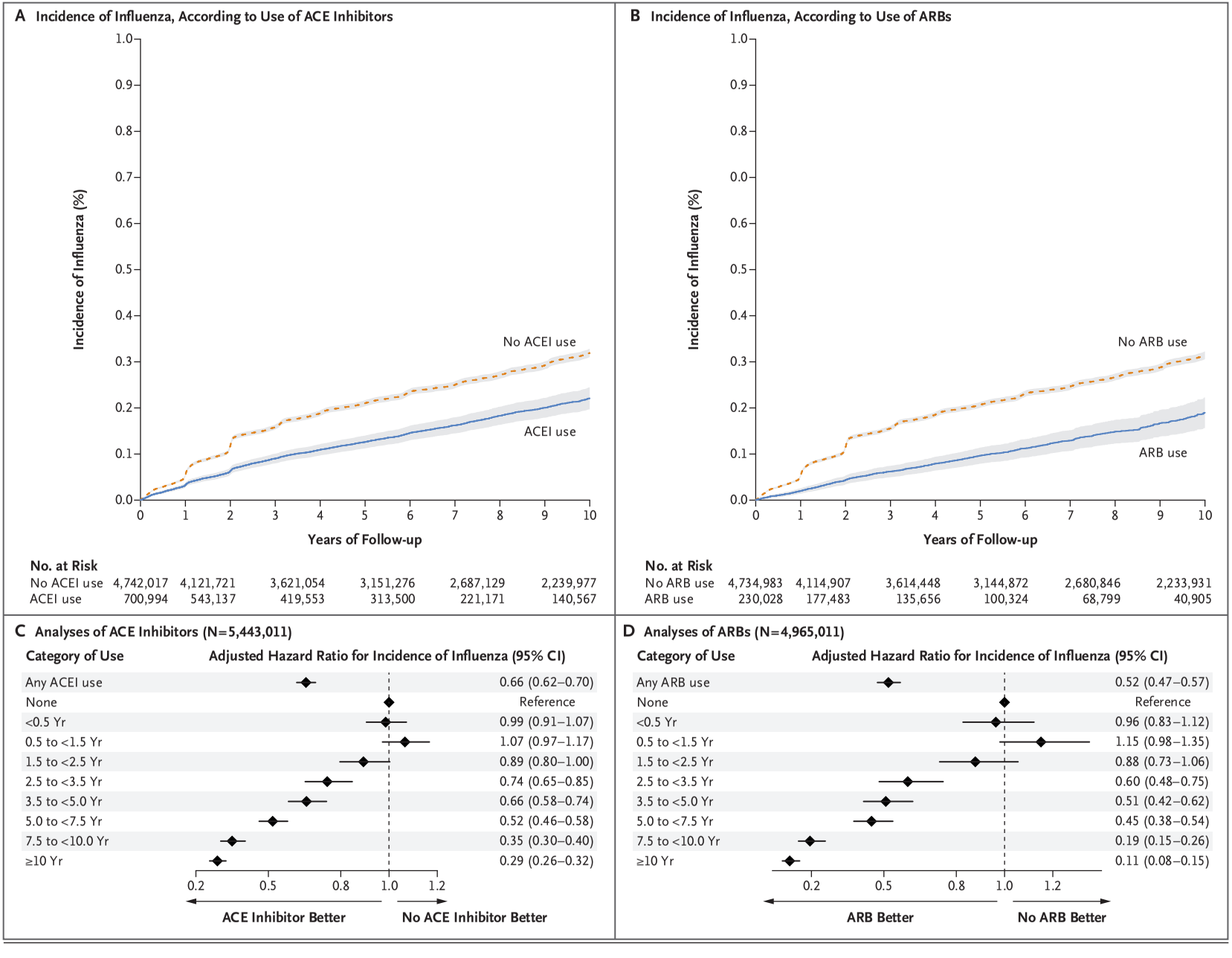

Figure 1 (facing page). Adjusted Kaplan–Meier Analyses and Hazard Ratios for Incident Influenza, According to Duration of Use of ACE Inhibitors and ARBs.

Shown is the incidence of influenza according to the use of an angiotensin-converting–enzyme inhibitor (ACEI) (Panel A) or angiotensin-receptor blocker (ARB) (Panel B). Also shown are hazard ratios for influenza in subgroups of persons who received a prescription for an ACE inhibitor (Panel C) or ARB (Panel D), according to the duration of use. All analyses have been adjusted for the age at baseline, sex, smoking history, presence of obesity, influenza vaccination, the presence of 12 coexisting conditions, and the time period of the influenza outbreak.

observed susceptibility to influenza may reflect mechanisms that are shared with coronaviruses, including SARS-CoV-2.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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