Conflict of Interest Disclosures: None reported.

1. Cowley NJ, Owen A, Shiels SC, et al. Safety and efficacy of antiviral therapy for prevention of cytomegalovirus reactivation in immunocompetent critically ill patients: a randomized clinical trial. *JAMA Intern Med*. 2017;177(6):774-783.

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In Reply We appreciate the interest shown in our Original Investigation.[1] Drs Navarro and Aguilar are correct to note that the small numbers of patients in whom we could obtain repeat bronchiolar lavage specimens makes conclusions on viral suppression in the lung difficult. We agree that the effective suppression of viremia may not necessarily exclude end organ disease.

In response to Drs De Vlieger and Van Wijngaerden, we agree that the question of whether cytomegalovirus (CMV) reactivation in critical illness is causal or consequential is an important issue. It is clear from the previous work of De Vlieger and colleagues[2] looking for correlations between CMV serostatus alone and mortality that indiscriminate use of antiviral prophylaxis in the CMV-seropositive ICU population would unlikely be of value. The cohort that they examined in their primary analysis[2] suffered from the inclusion of many low-risk and short-stay elective ICU admissions without evidence to support critical illness such as prolonged mechanical ventilation.[2] Although De Vlieger and colleagues went on to perform subgroup analyses of patients at higher risk of reactivation, these reduced numbers considerably, and an analysis with the exclusion of all low risk patients was not performed. Repeating this analysis in a larger cohort of patients who are critically ill may help to answer this question. Targeting more specific susceptible groups for antiviral prophylaxis, such as those with acute lung injury, may be answered by work recently completed by the American GRAIL study group (NCT01335932). The acyclovir arm in our study[1] was terminated early in our work, although recruitment continued in the control and ganciclovir arms. It would be premature to suggest that the excess mortality could be attributed to aciclovir, given its extensive record of clinical and research evaluation over many years, including in critically ill patients, the small numbers of patients in this study, and the attribution of cause of death to the underlying disease process by independent blinded reviewers.

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1. Cowley NJ, Owen A, Shiels SC, et al. Safety and Efficacy of Antiviral Therapy for Prevention of Cytomegalovirus Reactivation in Immunocompetent Critically Ill Patients: A Randomized Clinical Trial. *JAMA Intern Med*. 2017;177(6):774-783.

2. De Vlieger G, Meersseman W, Lagrou K, et al. Cytomegalovirus serostatus and outcome in nonimmunocompromised critically ill patients. *Crit Care Med*. 2012;40(1):36-42.

β-Blockers and Diltiazem Combination—Bear in Mind the Risk of Heart Block

To the Editor I read with interest the Teachable Moment by Carroll and Hassanin[1] published in a recent issue of *JAMA Internal Medicine* and concerning the worrisome issue of polypharmacy in the elderly. I fully agree with Carroll and Hassanin[1] about the opportunity of considering medication reconciliation and of containing the number of comedications in the elderly to a minimum. The strategies proposed by Carroll and Hassanin[1] (ie, use of established prescribing tools such as Beers criteria and STOPP criteria and/or discontinuation of medications without a clear indication) are robust and may surely concur in reducing polypharmacy. Likewise, they may be helpful in effectively preventing avoidable drug-drug interactions leading to unintentional hospital admission.

However, as a clinical pharmacologist, I would draw attention to an additional drug-drug interaction that has been underestimated in the case reported. The described presyncopal episode with bradycardia that occurred to the 83-year-old woman in the Teachable Moment[1] was attributed to an unintentional metoprolol overdose. Indeed, it should not be overlooked that 2 days before the patient suffered from an acute episode of atrial fibrillation with rapid ventricular response that was treated with metoprolol and diltiazem, a drug combination that may cause a severe drug-drug interaction. Noteworthy, the use of β-blockers in combination with nondihydropyridine calcium channel blockers, such as verapamil or diltiazem, is considered inappropriate in patients age 65 and older by the same STOPP criteria[2] that were recommended as helpful tool for deprescribing by Carroll and Hassanin themselves. As highlighted by the American Society of Hypertension in a position article[3] on combination therapy for hypertension published in 2010, clinicians should bear in mind that the additive effects of this drug combination on heart rate and atrioventricular conduction may result in severe bradycardia or heart block. Accordingly, concomitant use should be avoided.

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Conflict of Interest Disclosures: None reported.

Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

1. Carroll C, Hassanin A. Polypharmacy in the elderly-when good drugs lead to bad outcomes: a teachable moment. *JAMA Intern Med*. 2017;177(6):871.

2. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213-218.

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The Dangers of Polypharmacy in Elderly Patients

To the Editor In a recent issue of *JAMA Internal Medicine*, Carroll and Hassanin[1] published a Teachable Moment that embodies the importance for health care practitioners to reduce polypharmacy and prevent adverse drug events. Although we support their conclusions, we provide additional explanation regarding underlying causes of bradycardia and hypotension in patients besides unintentional metoprolol overdose.

A review of the patient's medication list as described in this Teachable Moment[1]—in the context of atrial fibrillation (AFib) with symptomatic bradycardia and hypotension—suggests a medication-induced atrioventricular (AV) heart block, and 4 factors support this proposition: (1) the patient was discharged with 3 drugs slowing AV nodal conduction (ie, digoxin, metoprolol and diltiazem); (2) no pharmacokinetic interaction is observed with metoprolol; (3) in contrast, pharmacokinetic interactions are observed with digoxin; (4) steady state plasma levels were not reached before discharge (especially for digoxin).

Ventricular rate control is often a preferred approach in patients with AFib. Therefore, the combined use of metoprolol, diltiazem, and digoxin, whether or not intended to control ventricular response in this patient, could clearly be associated with second and/or third degree AV block.

Metoprolol is primarily metabolized (80%) by the genetically determined polymorphic CYP2D6 enzyme. If the patient was previously able to tolerate metoprolol, it is unlikely that she poorly metabolizes CYP2D6 (experiencing unintentional metoprolol overdosing). Furthermore, she was not currently treated with other CYP2D6 substrates or inhibitors than may have caused phenoconversion. Instead, evidence supports a drug interaction with digoxin, a substrate of the P-glycoprotein (P-gp) drug-transporter. Medications that are P-gp inhibitors increase digoxin blood levels. Diltiazem and atorvastatin influence P-gp activity and competitively decrease P-gp-mediated renal secretion of digoxin.[2-5]

The patient described in this Teachable Moment[1] was discharged from the hospital prior to achieving steady state drug levels (4-5 drug elimination half-lives); thus, plasma levels were still increasing. Following reintroduction of drugs, time to reach a new steady state level, particularly for digoxin ($t_{1/2}$ ~ 26-45h), should have been considered.

Finally, potassium levels are modulated by both lisinopril and furosemide. These factors could have been considered to rule out toxic effects associated with digoxin. Ensuring therapeutic digoxin plasma levels would have been helpful to mitigate risk of toxic effects.

We propose that the adverse drug events experienced by this patient are not attributable to unintentional metoprolol overdose but most likely the result of a cumulative AV block by 3 drugs; 1 of them, digoxin, being the object of drug interactions potentially leading to toxic levels.

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Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

1. Carroll C, Hassanin A. Polypharmacy in the elderly-when good drugs lead to bad outcomes: a teachable moment. *JAMA Intern Med*. 2017;177(6):871.

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CORRECTION

Omission of Conflicts of Interest: In the article titled "Eliminating Creatine Kinase–Myocardial Band Testing in Suspected Acute Coronary Syndrome: A Value-Based Quality Improvement,"[1] conflicts of interest were omitted when the article was published online. The article was corrected online.

1. Alvin MD, Jaffe AS, Ziegelstein RC, Trost JC. Eliminating creatine kinase–myocardial band testing in suspected acute coronary syndrome: a value-based quality improvement. *JAMA Intern Med*. 2017;177(10):1-6.

Error in Author's Address: In the Viewpoint titled "Sharing and Healing Through Storytelling in Medicine," published online August 21, 2017,[1] an incorrect address was listed for the author. The contact information should have appeared as, "Emily Silverman, MD, Department of Internal Medicine, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110 (emily.silverman@ucsf.edu)." This article was corrected online.

1. Silverman E. Sharing and healing through storytelling in medicine [published online August 21, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2017.2996

Extraneous Sentence in the Abstract: In the Original Investigation titled "Association of Evidence-Based Care Processes With Mortality in *Staphylococcus aureus* Bacteremia at Veterans Health Administration Hospitals, 2003-2014,"[1] published online September 5, 2017, there was an extraneous sentence in the Results section of the abstract. This article has been corrected online.

1. Goto M, Schweizer ML, Vaughan-Sarrazin MS, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration hospitals, 2003-2014 [published online September 5, 2017]. *JAMA Intern Med*. 10.1001/jamainternmed.2017.3958