

## Medication Errors in Acute Cardiovascular and Stroke Patients: A Scientific Statement From the American Heart Association

Andrew D. Michaels, Sarah A. Spinler, Barbara Leeper, E. Magnus Ohman, Karen P. Alexander, L. Kristin Newby, Hakan Ay, W. Brian Gibler, Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation, Council on Cardiovascular Nursing and Stroke Council

*Circulation*. 2010;121:1664-1682; originally published online March 22, 2010;

doi: 10.1161/CIR.0b013e3181d4b43e

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2010 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circ.ahajournals.org/content/121/14/1664>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>

## Medication Errors in Acute Cardiovascular and Stroke Patients

### A Scientific Statement From the American Heart Association

Andrew D. Michaels, MD, MAS, FAHA, Chair; Sarah A. Spinler, PharmD, FAHA; Barbara Leeper, RN, MN, FAHA; E. Magnus Ohman, MD, FAHA; Karen P. Alexander, MD; L. Kristin Newby, MD, MHS; Hakan Ay, MD; W. Brian Gibler, MD, FAHA; on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Quality of Care and Outcomes Research; Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation; Council on Cardiovascular Nursing; and Stroke Council

Medical errors are the eighth leading cause of death in the United States and are estimated to account for somewhere between 44 000 and 98 000 deaths in the United States each year.<sup>1</sup> An exact number of deaths remains both uncertain and controversial, with arguments that the actual figure may be lower<sup>2</sup> or higher.<sup>3</sup> Each year in the United States, the estimated 450 000 preventable medication-related adverse events cost \$3.5 billion.<sup>4</sup> In the Health Grades Inc Patient Safety in American Hospitals study, which examined 37 million patient records, it was estimated that 195 000 Medicare patients die due to preventable, in-hospital medical errors annually.<sup>3</sup> Medication errors are the most common type of medical error, and cardiovascular medications prescribed to inpatients account for a large proportion of these errors. An average of 1 medication error occurs per hospitalized patient per day, and one quarter of all medication-related injuries are preventable. The emergency department (ED) and acute hospital setting remain locations at high risk for medication errors.

Since the Institute of Medicine's 2000 report, "To Err Is Human: Building a Safer Health System," there has been heightened awareness of medical and medication errors.<sup>1</sup>

In 2001, Congress appropriated \$50 million for major initiatives in patient safety and directed the Agency for Healthcare Research and Quality to establish the Center for Quality Improvement and Patient Safety. The following year, the American Heart Association (AHA) issued its first scientific statement on medication errors in acute cardiac care.<sup>5</sup> In 2003, Congress passed the Medicine Modernization Act to charge the Institute of Medicine with formulating a national agenda aimed at reducing medication errors. In these early years after the Institute of Medicine's report, the topic of patient safety became a frequent focus for healthcare leaders, journalists, and concerned citizens. Although significant advances have occurred regarding an understanding of the science and systems involved in medication errors, the building of a culture of safety has proved to be an immense task. Despite this public awareness and the research directed at the problem of medical errors, the impact of medication errors on patient safety remains a significant problem. The Institute of Medicine's update in 2006, entitled "Preventing Medication Errors," makes clear that medication errors still are a serious patient safety concern.<sup>4</sup> The present statement will examine common and serious medication

---

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 15, 2009. A copy of the statement is available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the "topic list" link or the "chronological list" link (No. KB-0034). To purchase additional reprints, call 843-216-2533 or e-mail [kelle.amsay@wolterskluwer.com](mailto:kelle.amsay@wolterskluwer.com).

The American Heart Association requests that this document be cited as follows: Michaels AD, Spinler SA, Leeper B, Ohman EM, Alexander KP, Newby LK, Ay H, Gibler WB; on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Quality of Care and Outcomes Research; Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation; Council on Cardiovascular Nursing; and Stroke Council. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. *Circulation*. 2010;121:1664-1682.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>. A link to the "Permission Request Form" appears on the right side of the page.

(*Circulation*. 2010;121:1664-1682.)

© 2010 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIR.0b013e3181d4b43e

errors in acute cardiovascular medicine, with a focus on strategies to reduce medication error frequency and consequences.

The writing group was charged with the task of performing an assessment of the evidence and giving a classification of recommendations and a level of evidence to each recommendation. The American College of Cardiology (ACC)/AHA classification system was used as follows:

### Classification of Recommendations

**Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

**Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

**Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.

**Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.

**Class III:** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

### Level of Evidence

**Level of Evidence A:** Data derived from multiple randomized clinical trials or meta-analyses.

**Level of Evidence B:** Data derived from a single randomized trial or nonrandomized studies.

**Level of Evidence C:** Only consensus opinion of experts, cases studies, or standard of care.

For the practice recommendations provided in this statement, the classification of recommendations and the level of evidence determinations were taken from data available from clinical trials or registries about the usefulness/efficacy in different subpopulations. A recommendation with level of evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials may not be available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and allow queries at the individual recommendation level.

### Medication Error Definition and Categories

A medication error may be defined broadly as events "... related to professional practice, healthcare products, procedures, and systems, including prescribing; order communica-

tion; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."<sup>6</sup> This definition is used by the US Pharmacopeia, the US Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services. Variations in definitions and abilities to uncover errors have contributed to a wide range in estimates of medication error rates. In the present statement, medication errors will include the following: Improper dosing or timing, delivery of an incorrect or unnecessary medication, administration to the wrong patient (errors of commission), and failure to prescribe appropriate medication therapy or needed monitoring of medication therapy (errors of omission).

### Medication Type Errors

To understand and successfully address the problem of medication errors, universal and standardized reporting mechanisms are essential. The US Pharmacopeia's MEDMARX is an anonymous, Internet-accessible program used nationwide by hospitals and related institutions to report, track, and analyze medication errors. In the MEDMARX 2006 report, similar medication names increased the rate of medication errors. As shown in Table 1, errors were higher among the more than 26 000 records with look-alike and/or sound-alike medication names than among other categories.<sup>7</sup> In addition to confusion regarding the medication name, there may be errors related to the selection of an incorrect medication formulation. For example, several antihypertensive and antianginal medications frequently come in various formulations for immediate versus sustained release, including nifedipine, diltiazem, verapamil, metoprolol, carvedilol, and nitrates. In addition, it has become increasingly recognized that acute administration of specific medications may cause QT-interval prolongation, which leads to an increased risk of torsade de pointes.<sup>8</sup> Failure to appropriately monitor the QT interval and adjust therapy in patients receiving QT-prolonging medications constitutes a medication error.

### Medication Dosing, Dispensing, and Timing Errors

Anticoagulants, narcotics, and insulins are high-alert medications identified by the Institute for Healthcare Improvement and the Institute for Safe Medication Practices.<sup>9</sup> The Joint Commission describes high-alert medications as those that have the highest risk of causing injury when misused. Medications in this class are most likely to cause significant harm to the patient, even if used as intended. Although mistakes may not be more common in the use of these medications, when errors occur, the impact to the patient may be significant. Other investigators have also identified anticoagulants and antiplatelet agents, commonly used in acute cardiovascular disease management, as among the medication groups that account for the majority of medication errors related to preventable hospital admissions.<sup>10,11</sup> These agents may increase the risk for harm when used inappropriately in patients hospitalized for acute cardiovascular disorders. One of the 2009 National Patient Safety Goals identified by The Joint

**Table 1. Selected Similar Medication Names in Acute Cardiovascular Practice**

Medication	Confused Medication Name
<i>Accupril</i> (ACE inhibitor)	<i>Aciphex</i> (proton pump inhibitor)
<i>Activase</i> (fibrinolytic)	<i>TNKase</i> (fibrinolytic)
<i>Aggrastat</i> (GP IIb/IIIa inhibitor)	<i>Argatroban</i> (thrombin inhibitor)
Calcium chloride	Calcium gluconate
Captopril (ACE inhibitor)	Carvedilol ( $\beta$ -adrenergic blocker)
<i>Cardene</i> (calcium channel blocker)	<i>Cardizem</i> (calcium channel blocker)
	<i>Cardura</i> ( $\alpha$ -adrenergic blocker)
Dobutamine (sympathomimetic)	Dopamine (sympathomimetic)
Epinephrine (inotrope)	Ephedrine (inotrope)
Isosorbide mononitrate (nitrate)	Isosorbide dinitrate (nitrate)
<i>Lanoxin</i> (digoxin)	Levothyroxine (thyroid)
Metoprolol tartrate ( $\beta$ -adrenergic blocker)	Metoprolol succinate ( $\beta$ -adrenergic blocker)
Nicardipine (calcium channel blocker)	Nifedipine (calcium channel blocker)
Norepinephrine (inotrope)	Neo-synephrine ( $\alpha$ -adrenergic agonist)
Pindolol ( $\beta$ -adrenergic blocker)	<i>Plendil</i> (ACE inhibitor)
<i>Plavix</i> (antiplatelet)	<i>Paxil</i> (antidepressant)
Pravachol (HMG-CoA reductase inhibitor)	Propranolol ( $\beta$ -adrenergic blocker)
Protamine (heparin reverser)	Protonix (proton pump inhibitor)
<i>Tiazac</i> (calcium channel blocker)	<i>Ziac</i> ( $\beta$ -adrenergic blocker and diuretic)
<i>Toprol-XL</i> ( $\beta$ -adrenergic blocker)	<i>Topamax</i> (migraine prophylaxis)
<i>Tricor</i> (hypolipidemic)	<i>Tracleer</i> (endothelin antagonist)
Valsartan (AT2 receptor antagonist)	Losartan (AT2 receptor antagonist)
<i>Zebeta</i> ( $\beta$ -adrenergic blocker)	<i>DiaBeta</i> (hypoglycemic)

ACE indicates angiotensin-converting enzyme inhibitor; GP, glycoprotein; HMG-CoA, hydroxymethylglutaryl coenzyme A; and AT2, angiotensin II type 2 receptor.

Information adapted in part from the Institute for Safe Medication Practices' "List of Confused Drug Names," available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>.

Brand names are italicized.

Commission is to improve the safety of medication use by focusing on reducing the likelihood of harm from anticoagulation.

### Medication Omission Errors

Omission of life-saving medications is an underrecognized medication error in the management of patients with acute cardiovascular disease. The proportion of reperfusion-eligible patients presenting with ST-segment elevation myocardial infarction (STEMI) who received immediate reperfusion therapy (either fibrinolytic medications or primary percutaneous coronary intervention) remained only 71% in 2006.<sup>12</sup> Failure to prescribe adjunctive therapies, including antiplatelet agents,<sup>13</sup>  $\beta$ -blockers,<sup>14</sup> angiotensin-converting enzyme inhibitors,<sup>15</sup> and cholesterol-lowering agents,<sup>16</sup> for patients with acute coronary syndrome (ACS) is another example of an error of medication omission.

### Errors in the ED

Each year, more than 115 million patients seek care in EDs across the United States. This is the equivalent of 219 ED visits each minute, based on a National Hospital Ambulatory Medical Care Summary.<sup>17</sup> MEDMARX received reports of 29 801 medication errors in EDs from 2002 to 2006. MEDMARX studies showed that 53% of medication errors reached ED patients (in the remaining 47% of cases, the errors were recognized or the medication was not given), 13% of these caused potential harm, and 3% of these resulted in definite harm or death. Substantial patient overcrowding in many EDs, high provider turnover, and language barriers provide an environment that can increase the risk of medication errors. Therefore, simple processes such as adhering to the ACC/AHA guidelines tend to be less effective among EDs where resources are underfunded.<sup>18,19</sup> Caring for critically ill and injured patients with limited information regarding the medical history of the patients also creates a high-pressure environment in which errors in both type and dosage of medications may be more frequent. Finally, the transition of care from one emergency physician to another emergency physician at changes of shift (or from emergency physician to inpatient physician at the time of admission) is a particularly vulnerable time in medical communication that may result directly in medication errors.<sup>20</sup> Medication errors to which ED patients are particularly prone include failure to identify known allergies, failure to identify current outpatient medications that could interact with those provided in the ED, inappropriate type or dosing of medications, incorrect route for administration, an incomplete understanding of variability in dosing for patients with renal insufficiency or diabetes mellitus, and excess dosage for a given body weight, particularly in older women.

### Patient Subgroups at High Risk for Errors

#### Older Adults

Older adults are at a higher risk of medication errors and have a greater propensity for experiencing harmful and fatal errors.<sup>21</sup> The most common types of medication errors among the elderly are those of omission (26%) and improper dose (26%). The use of aspirin, fibrinolytic agents, and heparin acutely and of statins at discharge remains suboptimal even among ideal older adults with acute myocardial infarction with indications for these medications and no contraindications to their use.<sup>22,23</sup> Medication errors of omission are also more likely to occur in elderly patients with ACSs considered to be secondary to another diagnosis. These secondary ACS events are independent predictors of the lack of recommended medication therapy.<sup>24</sup> Omission of evidence-based medications that results from reasonable clinical judgment are of little concern compared with those due to misdiagnosis or misclassification of risk and benefit among those eligible for treatment.

In a population study from 15 000 hospital discharges in 1992, those  $\geq 65$  years of age had twice the rate of preventable adverse medication events as those 16 to 64 years old

(5.3% versus 2.8%,  $P=0.001$ ); however, in multivariable analysis adjusted for comorbidity and case mix, age was not independently associated with preventable adverse events.<sup>25</sup> Rather, older adults are at risk for medication errors for other age-associated reasons. There are very few cardiovascular medications for which doses are adjusted by age alone. In fact, most cardiovascular medication errors in older adults are omission errors.<sup>26</sup>

High rates of polypharmacy also increase the likelihood of drug-drug interactions. Older adults are less likely to receive appropriate follow-up laboratory monitoring for 1 or more of their medications, including angiotensin-converting enzyme inhibitors, amiodarone, and statins.<sup>27</sup> There are age-related changes in pharmacokinetics (eg, medication absorption, metabolism, and hepatic or renal elimination) and pharmacodynamics (eg, reduced baroreflexes and receptor responsiveness), both of which necessitate dose adjustments or heighten susceptibility to medication adverse events. Age tends to be a surrogate for worse renal function, which is important for medications that are cleared renally. Rapid dose escalation may take place during the brief period of acute cardiac hospitalization in an older adult who is also supine and eating a hospital diet, which undermines the advice of “start low, go slow.” In addition, the one-size-fits-all approach to dosing of adjustable anticoagulants results in excess dosing disproportionately affecting older adults and contributes to excess major bleeding.<sup>28</sup>

**Chronic Kidney Disease**

The estimation of creatinine clearance is one of the most important factors that should be readily available to any healthcare provider who prescribes medicines, both in the emergency and the in-hospital setting. Medications such as enoxaparin, eptifibatide, tirofiban, bivalirudin, dofetilide, and sotalol are dosed on the basis of estimated creatinine clearance (eCrCl) with the Cockcroft-Gault formula,<sup>29</sup> not based on the estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula.<sup>30</sup> The 2007 unstable angina/non-STEMI practice guidelines recommend adjusting doses of renally cleared cardiovascular medication on the basis of the eCrCl.<sup>31</sup> The clinical studies and labeling that define adjustments for cardiovascular medication have been based on the Cockcroft-Gault formula, which is not identical to the Modification of Diet in Renal Disease equation. According to the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) study, clinically important disagreements between eCrCl and estimated glomerular filtration rate occurred in one fifth of ACS patients; the authors concluded that medication dosing should be based on the Cockcroft-Gault formula.<sup>32</sup> Although use of the Cockcroft-Gault formula is recommended by the present writing group, this topic remains controversial, because the National Kidney Foundation<sup>33</sup> and the National Kidney Disease Education Program<sup>34</sup> have recommended using either eCrCl or estimated glomerular filtration rate for drug dosing.

Ideally, the eCrCl should be calculated automatically for all creatinine measurements so that eCrCl is provided in addition to the estimated glomerular filtration rate and serum creatinine result. An even more sophisticated system would function such that when electronic prescribing takes place in the hospital, the latest eCrCl would be displayed automatically for all patients for whom a medication was prescribed that requires renal adjustment.<sup>35</sup>

Patients with chronic kidney disease are more susceptible to nephrotoxicity from iodine-based angiographic and gadolinium-based magnetic resonance imaging contrast studies. Strategies to prevent contrast-induced nephrotoxicity should be used for patients undergoing x-ray angiography or computed tomography with iodine-based contrast.<sup>36</sup> The FDA has recently issued a public health advisory stating that exposure to gadolinium-based contrast agents increases the risk for nephrogenic systemic fibrosis in patients with acute or stage IV chronic kidney disease (glomerular filtration rate <30 mL/min) or acute renal insufficiency of any severity.<sup>37</sup> It has been suggested that strategies to prevent contrast-induced nephrotoxicity or an alternative imaging method be considered in patients with stage IV or V chronic kidney disease who undergo angiography with an iodine-based contrast agent or magnetic resonance imaging with a gadolinium-based contrast agent.

**Weight-Based Medication Dosing**

Although patients admitted to the intensive care unit can be weighed accurately with hospital bed scales, this is not practical for a significant proportion of critically ill patients presenting to the ED. Accurate weight assessment is a challenge for ED patients who are incapacitated. Because many acute cardiovascular medications are dosed according to actual (and not ideal) body weight, overestimation and underestimation of body weight constitute an important source of medication errors that result in adverse medication events and ineffectiveness, respectively. Examples of acute cardiovascular medications that require accurate weight assessment include unfractionated heparin, low-molecular-weight heparin, glycoprotein IIb/IIIa receptor antagonists, fibrinolytic agents (eg, alteplase and tenecteplase), inotropes (eg, dobutamine), vasopressors (eg, dopamine and norepinephrine), vasodilators (eg, nesiritide and nitroprusside), and the inodilator milrinone.

Several studies have examined the accuracy of patients, paramedics, nursing staff, and medical staff in estimating weight in patients brought to the ED. In 1 study, although patients had a mean absolute error of only 3 kg in their estimation of body weight, paramedics, nurses, residents, and attending physicians had a mean absolute error of 9 to 10 kg.<sup>38</sup> Although only 1.5% of patient weight estimations were more than 20% off, 13% to 17% of healthcare providers’ estimations were inaccurate by more than 20%. Other studies agree that weight estimation by medical staff is a potential contributor to medication errors.<sup>39,40</sup> These errors are more pronounced in patients at extremes of body weight.

In critically ill obese patients, noninvasive blood pressure assessment is not reliable. In hypotensive and hypertensive obese patients in the acute care setting, noninvasive blood pressure recordings tend to be inaccurate, which leads to erroneous interpretations of blood pressure and potentially could lead to treatment errors with vasopressors or antihypertensive medications. One study used direct radial arterial blood pressure measurement as the gold standard, and noninvasive blood pressure measurement by the auscultatory technique (calibrated aneroid manometer) significantly overestimated the true blood pressure.<sup>41</sup> Automated noninvasive blood pressure measurements with the oscillometric technique significantly underestimate blood pressure in hypertensive patients. Therefore, in critically ill obese patients, invasive blood pressure monitoring should be instituted rapidly in the critical care setting.

## Disease-Based Considerations in Risk for Medication Errors

### Acute Coronary Syndrome

The most common types of medication errors in this group include medication dose errors (including failure to account for renal dysfunction), omission (failure to either give the medication or to resume treatment), and miscalculation of a patient's weight. In STEMI patients, omission errors are represented dramatically by the relatively low rates of use of immediate reperfusion therapy,<sup>12</sup> aspirin,<sup>42</sup> clopidogrel, angiotensin-converting enzyme inhibitors,<sup>15</sup>  $\beta$ -blockers, and statins during hospitalization.<sup>43</sup> For the acute administration of intravenous  $\beta$ -blockers in STEMI patients, guideline recommendations have changed recently.<sup>44</sup> Because of an increased risk of cardiogenic shock in patients treated with intravenous  $\beta$ -blockers, current recommendations now advise the avoidance of therapy in patients with any signs of heart failure and in those at increased risk of developing heart failure. What previously may have been considered an error of omission may now be considered a medication error if intravenous  $\beta$ -blocker therapy is given to a patient with evidence of heart failure, because of the increased risk of cardiogenic shock.

The non-STEMI population tends to be an older population with greater comorbid illnesses, worse renal function, and a higher proportion of women. These characteristics predispose to untoward medication reactions if appropriate dosing adjustments are not made. In a comprehensive analysis from the CRUSADE National Quality Improvement Initiative evaluating excessive dosing in patients with non-ST-elevation ACS, 42% of patients who were administered an antithrombotic agent received at least 1 initial dose outside the recommended range.<sup>23</sup> The excess dosing was seen with unfractionated heparin (33%), low-molecular-weight heparin (14%), and glycoprotein IIb/IIIa inhibitors (27%). The factors associated with excessive dosing included older age, female sex, renal insufficiency, low body weight, diabetes mellitus, and congestive heart failure. It was estimated that 15% of all

major bleeding in this population was attributable to excessive dosing.

The latest quality metrics for patients with acute myocardial infarction include the frequency of excessively dosed heparin, low-molecular-weight heparin, and glycoprotein IIb/IIIa inhibitors; omission of clopidogrel in medically managed patients; the presence of a weight-based heparin-dosing protocol; and the ability to track bleeding events related to anticoagulants.<sup>45</sup> Systems approaches, such as the AHA's evidence-based Get With The Guidelines, have been shown to improve adherence to guidelines, with an emphasis on reducing medication errors of omission and commission.<sup>46</sup> The following section highlights errors in prescribing that are related to specific agents in ACS (Table 2).

### Antiplatelet Agents

The dose of aspirin in combination with other antiplatelet and antithrombotic agents is an important topic. The Second International Study of Infarct Survival (ISIS-2) used a 162.5-mg dose, whereas the most commonly prescribed dose in the United States is 325 mg.<sup>47</sup> Observational data suggest that the use of a lower dose of aspirin (81 mg) after discharge for ACS may be safer, particularly when combined with clopidogrel or prasugrel.<sup>48</sup> Although higher doses may be important in the immediate percutaneous coronary intervention setting, the use of lower doses of aspirin might be appropriate when aspirin is used with clopidogrel, because the higher dosing may be associated with more bleeding.<sup>49</sup> Although the recently presented results of the CURRENT-OASIS 7 trial (Clopidogrel optimal loading dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for InterventionS) found no differences in ischemic or bleeding outcomes at 30 days in an ACS population with low-dose versus high-dose aspirin,<sup>50</sup> that study did not assess the impact of aspirin dose on longer-term bleeding risks with dual-antiplatelet maintenance therapy.

Another area of complexity in aspirin dosing occurs when patients state that they are allergic to aspirin. Although 3% to 4% of patients have been identified as intolerant to aspirin, closer evaluation suggests that only about half are truly allergic to aspirin.<sup>51</sup> Errors of omission that occur when aspirin is withheld in patients who are simply intolerant to aspirin could be avoided with accurate reporting. For those patients with documented allergy to aspirin, desensitization may be an attractive alternative compared with omission.

The frequency of clopidogrel omission in the management of ACS patients has been reported recently. The proportion of non-STEMI patients treated with clopidogrel within 24 hours of admission who did not undergo early percutaneous coronary intervention has increased from 30% in 2002 to 50% in 2005.<sup>52</sup> Adjusted in-hospital mortality was lower in those treated with clopidogrel.

Intravenous glycoprotein IIb/IIIa inhibitors have been a major advancement in ACS management. Even among diverse randomized trials, women and older adults have higher bleeding rates.<sup>53</sup> Up to one fourth of the bleeding risk

**Table 2. Common Medications Errors in Patients With ACS**

Medication	Type of Error	Reason for Use	Preventable Adverse Event	Guideline Recommendations <sup>31,44</sup>
Aspirin	Underuse; misuse (errors in dosing)	Primary and secondary infarction prevention	Increased risk of thrombotic and hemorrhagic complications	Discriminate between true aspirin allergy vs intolerance. Consider dose reduction in patients taking clopidogrel.
$\beta$ -Blocker	Overuse; misuse (errors in dosing, patient selection, timing)	Prevention of reinfarction and arrhythmia	Increased risk of cardiogenic shock, bradyarrhythmias	In STEMI patients, avoid early IV $\beta$ -blockers in those with hypotension, pulmonary congestion, or PR prolongation and those at increased risk for cardiogenic shock.
Heparin	Misuse (errors in dosing, monitoring, prescribing, transcribing)	Prevention of early reinfarction and infarction progression	Increased risk of hemorrhagic complications	Weight-based dosing algorithms, particularly important when coadministered with fibrinolytics and GP IIb/IIIa inhibitors.
Low-molecular-weight heparin	Misuse (errors in dosing, monitoring, prescribing)	Primary and secondary infarction prevention	Increased risk of thrombotic and hemorrhagic complications	Careful dosing in obese patients and those with renal insufficiency. Ensure proper dosing (IV and subcutaneous) for STEMI patients.
Small-molecule GP IIb/IIIa inhibitor	Misuse (errors in dosing, monitoring, prescribing, transcribing)	Prevention of early reinfarction and infarction progression	Increased risk of thrombotic and hemorrhagic complications	Follow recommended bolus and infusion dose reductions in patients with renal insufficiency for eptifibatid (creatinine clearance <50 mL/min) and tirofiban (creatinine clearance <30 mL/min). In obese patients, prescribe on the basis of labeled dosing recommendations for obese patients.
Direct thrombin inhibitor	Misuse (errors in dosing)	Primary and secondary infarction prevention	Increased risk of thrombotic and hemorrhagic complications	For bivalirudin, follow recommended dose reductions in patients with renal insufficiency (creatinine clearance <30 mL/min). Dosing varies for PCI and medical therapy for ACS.
Factor Xa inhibitor	Misuse (errors in dosing)	Primary and secondary infarction prevention	Increased risk of thrombotic and hemorrhagic complications	Fondaparinux is contraindicated if creatinine clearance <30 mL/min.
Fibrinolytic	Underuse (errors of omission); misuse (errors in dosing, patient selection, timing)	Prevention of infarction progression	Failure to achieve reperfusion; increased risk of hemorrhagic complications	Ensure dosing corresponds to proper fibrinolytic (ie, avoid confusing dosing of TNKase and that of tPA).

IV indicates intravenous; PCI, percutaneous coronary intervention; and tPA, tissue plasminogen activator.

difference observed in women is avoidable and attributed to excessive dosing in women.<sup>54</sup> Women receiving glycoprotein IIb/IIIa inhibitors were more likely to receive excessive doses than men (46% versus 17%,  $P < 0.0001$ ).

**Fibrinolytic Agents**

Incorrect dosing of fibrinolytic agents has been reported to occur in 5% to 12% of STEMI patients.<sup>55</sup> The dosing regimens vary significantly for each of the available fibrinolytic drugs, including streptokinase, tissue plasminogen activator (alteplase), reteplase, and tenecteplase. Dosing errors in the Global Use of Strategies To Open occluded arteries (GUSTO)-I trial were 13.5% for streptokinase and 11.5% for alteplase.<sup>56</sup> Importantly, 30-day mortality was higher in those with medication errors for both fibrinolytic agents and placebo dosing. In contrast, dosing errors are significantly lower for the double-bolus agent reteplase and the single-bolus agent tenecteplase.<sup>54,57</sup>

In the ASsessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial, incorrect dosing occurred in 4.9% of patients receiving alteplase and 3.6% of those receiving tenecteplase.<sup>58</sup> For those treated with tenecteplase, underdosing occurred in 3.1%, whereas overdosing

occurred in 1.5%. Compared with those receiving the correct fibrinolytic dose, patients who received underdosing or overdosing were more likely to be older, to be female, to have lower body weight and systolic blood pressure, and to have a higher Killip class, all of which are associated with higher risk. After adjustment for confounding baseline characteristics, alteplase overdosing was no longer associated with higher mortality, in-hospital stroke, or in-hospital major bleeding. Even with accounting for confounding variables, there is a narrow therapeutic window for fibrinolytic agents, with the potential for adverse outcomes in those with dosing errors. Importantly, although fibrinolytic dosing errors need to be minimized, caution should be exerted in concluding that adverse outcomes associated with errors are directly attributable to the dosing errors. Dosing errors for fibrinolytic agents may reflect other systems and performance deficits that may be associated with increased mortality.

**Anticoagulant Agents**

Anticoagulants account for 4% of preventable adverse medication events and 10% of potential adverse medication events.<sup>59</sup> Nearly half (49%) of fibrinolytic-treated STEMI patients receive an excess dose of unfractionated heparin in

contemporary practice.<sup>60</sup> Excess dosing is more common in females and those with low body weight.<sup>28</sup> Patients who receive excessive heparin have higher rates of major bleeding and transfusion.<sup>28</sup>

The ACC/AHA guidelines recommend weight-based unfractionated heparin dosing for non-STEMI<sup>31</sup> and STEMI<sup>44</sup> (with fibrinolytic drugs) ACS with an initial intravenous bolus of 60 U/kg (maximum 4000 U) and an infusion of 12 U · kg<sup>-1</sup> · h<sup>-1</sup> (maximum 1000 U/h). An important source of dosing error for unfractionated heparin in ACS patients is the higher recommended dosing for patients with acute pulmonary embolism (an initial intravenous bolus of 80 U/kg with a 5000-U maximum, and an infusion of 18 U · kg<sup>-1</sup> · h<sup>-1</sup> with a 1300-U/h maximum)<sup>61</sup> and the absence of a bolus dose of unfractionated heparin in stroke patients. In the CRUSADE Quality Improvement Initiative, an excess weight-adjusted unfractionated heparin bolus or infusion was administered 35% of the time.<sup>28</sup> The factors most strongly associated with excess weight-adjusted dosing were older age and female sex. The rate of major bleeding increased proportionally in relation to the dose of unfractionated heparin for both bolus and infusion.<sup>32</sup> These data suggest that closer attention should be paid to dosing by weight rather than using standard bolus therapy and infusion.

Enoxaparin dosing is adjusted on the basis of both weight and eCrCl. Dosing of enoxaparin for patients with STEMI or those undergoing percutaneous coronary intervention includes both intravenous and subcutaneous administration. Variation in enoxaparin administration practices may lead to confusion when ACS patients are treated in the ED or an outside hospital and then transferred to the cardiac catheterization laboratory or another facility for further management. Because there is no widely available point-of-care laboratory test to assess the level of enoxaparin anticoagulation (comparable to the activated clotting time for unfractionated heparin), low-molecular-weight heparin–dosing errors may arise when it is difficult to confirm the dose, route, and timing of administration.

In the CRUSADE Quality Improvement Initiative, 19% of patients treated with enoxaparin received an excess dose, whereas 29% received a lower-than-recommended dose.<sup>62</sup> Patients who did not receive the appropriate dose had worse outcomes, particularly those who received an excessive dose. Again, patients receiving excessive doses were older, smaller, and more likely to be female than patients who received recommended dosing. To date, there has not been sufficient published information regarding dosing errors with other anticoagulants such as fondaparinux and bivalirudin, which are both dose adjusted for renal function. Recently, The Joint Commission National Patient Safety Goal for 2008 aimed at improving the safety of therapeutic anticoagulation in hospitalized patients (Table 3).<sup>63</sup>

### Statins

Omission medication errors involving statins are common in patients with ACS.<sup>16</sup> Similar to other classes of agents for ACS management, the initiation of statin therapy in the hospital improves both outcomes and long-term adherence.<sup>64</sup>

Simvastatin, atorvastatin, and lovastatin (but not pravastatin or rosuvastatin), for example, are substrates for metabolism by the 3A4, 3A5, and 3A7 P450 cytochromes. Medication interactions may result in increased statin concentrations caused by inhibitors of this cytochrome (ie, diltiazem, verapamil, amiodarone, clarithromycin, and ketoconazole), whereas inducers (ie, phenytoin, pioglitazone, troglitazone, rifampin, and St. John's wort) of this hepatic pathway may reduce statin levels.

Recently, the FDA issued a warning regarding a dose-dependent drug interaction for the coadministration of simvastatin and amiodarone.<sup>65</sup> Although simvastatin has had this warning included in its label since 2002, reports continue to occur related to the increased risk of life-threatening rhabdomyolysis when simvastatin in doses greater than 20 mg daily is coadministered along with amiodarone, leading to elevated simvastatin concentrations. Amiodarone, as well as verapamil and cyclosporine, reduces the clearance of simvastatin up to 4-fold. In patients with acute myocardial infarction, simvastatin is often prescribed in high doses acutely. These patients may have already been prescribed amiodarone before admission, or during admission, for management of supraventricular and/or ventricular tachyarrhythmias.

### Acute Heart Failure

Management of the patient with acute decompensated heart failure is one of the most complex medical situations encountered in acute cardiovascular care, yet there is a paucity of literature specifically on medication errors in treating acute heart failure. Despite this, common sense suggests that medication errors are common in these critically ill patients, and the issues and strategies outlined in the present document are applicable to this area of cardiovascular care.

Patients with heart failure are prone to polypharmacy and its associated issues with dosing, timing, and drug-drug interactions. For example, digoxin serum concentrations may be increased by many medications, including antiarrhythmic agents such as amiodarone and dronedarone. In addition, as patients transition from stable heart failure to acute heart failure, institution of vasopressor or inotrope therapy may be necessary. In this setting, care should be taken to decrease or stop dosages of  $\beta$ -blockers or angiotensin-converting enzyme inhibitors in the face of hypotension. Careful monitoring of potassium and magnesium concentrations, as well as renal function, is important for patients receiving diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and aldosterone inhibitors.<sup>66</sup> Use of standard dosing units in patients receiving intravenous vasodilators, inotropes, and vasopressors may reduce the risk of dosing errors. For example, 2 different norepinephrine infusion dosing recommendations exist: Micrograms per kilogram per minute<sup>67</sup> and micrograms per minute.<sup>68</sup> The existence of 2 different dosing units (one based on body weight and another not based on body weight) for this medication is a source of critical medication dosing errors, resulting in an error (2 orders of magnitude for adults) of dose administration.



**Table 3. Improving Safety of Therapeutic Anticoagulation: Recommendations From The Joint Commission<sup>112</sup> and the Institute for Healthcare Improvement<sup>115</sup>**

<p>General recommendations</p> <ul style="list-style-type: none"> <li>Use standard concentrations in ED, OR, cardiac catheterization laboratory, and ICU.</li> <li>Separate like products when using or storing.</li> <li>Use smallest package, concentration, and dose for floor stock.</li> </ul> <p>Anticoagulation recommendations</p> <ul style="list-style-type: none"> <li>Format anticoagulation flow sheets and orders to follow the patient through transitions from hospital to skilled care and to home.</li> <li>Use a centralized anticoagulant dosing service for inpatients and have a specialized outpatient anticoagulation clinic.</li> <li>Implement a weight-based heparin protocol.</li> <li>Use preprinted order forms or ordering protocols for heparin and low-molecular-weight heparin.</li> <li>Ensure that heparin cannot be administered within 6 to 12 hours of a low-molecular-weight heparin dose.</li> <li>Dispense the anticoagulant medication from pharmacy only.</li> <li>Establish guidelines to hold heparin and provide reversal therapy for heparin overanticoagulation.</li> <li>Minimize available concentrations of heparin and warfarin.</li> <li>Develop standardized protocols for the initiation and maintenance of warfarin therapy, including vitamin K dosing guidelines for reversal of overanticoagulation.</li> <li>Develop a bridging protocol, based on evidence, to discontinue and restart warfarin perioperatively/periprocedurally.</li> <li>Engage patients in oral anticoagulation management by ensuring that they understand how to take warfarin, know other medications that should be avoided, and can identify symptoms that indicate harm.             <ul style="list-style-type: none"> <li>Develop educational programs and training, at an appropriate literacy level, to include self-monitoring and how to avoid medication and food interactions.</li> <li>Work with patients to have them carry an accurate list of medications all the time.</li> </ul> </li> <li>Use medication reconciliation to improve handoffs of medication information, such as follow-up INR monitoring when discharging a patient in need of warfarin INR monitoring.</li> <li>Make information available on laboratory results of coagulation tests such as aPTT, ACT, and INR to determine doses.             <ul style="list-style-type: none"> <li>Make laboratory results available on the unit within 2 hours, or monitor at the bedside.</li> <li>Plot INR results vs dose changes on run chart or control chart to improve dosing of warfarin.</li> </ul> </li> <li>Ensure appropriate monitoring and dose management through a centralized inpatient anticoagulation service.</li> </ul>
--

OR indicates operating room; ICU, intensive care unit; INR, international normalized ratio; aPTT, activated partial thromboplastin time; and ACT, activated clotting time.

Patients with acute heart failure, even in the absence of cardiogenic shock, are subject to altered renal and/or hepatic function that may modulate the renal clearance and/or metabolism of medications such as digoxin, lidocaine, milrinone, and statins and anticoagulant and antiplatelet therapies such as low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and warfarin, which may be used in patients with ischemic heart failure. Therefore, careful attention to changes in renal and hepatic function

and dose adjustment based on these parameters is essential. With acutely impaired renal function, hyperkalemia may ensue, particularly in the setting of use of aldosterone antagonists, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers. It may be necessary to withhold these agents until renal function improves. In contrast, aggressive diuresis should also lead to vigilance for hypokalemia and hypomagnesemia to avoid arrhythmias and adverse medication effects. Lastly, medication errors occur while heart failure patients are being transitioned back to the outpatient setting. Because heart failure medications are titrated rapidly during hospitalization, accurate prescriptions that pay attention to dosing, electrolyte management, and monitoring of renal function are important shortly after discharge.<sup>69</sup> It is well accepted that the institution of optimal heart failure pharmacological therapy during hospitalization is associated with improved outpatient adherence.<sup>70,71</sup>

### Acute Stroke

Although published data are limited, the available information suggests that medication errors are common among patients hospitalized for acute ischemic stroke. A retrospective evaluation based on chart review from 234 ischemic and hemorrhagic stroke cases revealed a 19% in-hospital incidence rate of medication errors.<sup>72</sup> Another study of 1440 patients with ischemic stroke that analyzed spontaneously reported errors and adverse events gathered within a voluntary and mandatory event-reporting system found that only 4% of the patients experienced an adverse event due to medication errors during hospitalization.<sup>73</sup> The mean length of hospital stay was 3 times longer in stroke patients with medical adverse events (including medication errors) than among patients who did not develop an adverse event.

Stroke is a severe medical condition that demands involvement of providers from multiple disciplines, including emergency physicians, stroke specialists, radiologists, vascular surgeons, nurses, imaging and laboratory technicians, and pharmacists. Failure of communication and coordination appears to be an important source of medication error.<sup>74,75</sup> In addition, there are various factors that are associated with increased vulnerability to medication errors in stroke populations. These include advanced age, altered level of consciousness, impaired communication because of aphasia, invasive nature of diagnostic evaluations, high prevalence of comorbid conditions, coadministration of multiple medications, use of intravenous route of administration because of impaired oral intake, administration of medications that require frequent laboratory testing and dose adjustments, and long hospital stay. Specific examples of medication errors for which stroke practice guidelines constantly report cautionary notes are presented in Table 4.

Intravenous alteplase is currently the only FDA-approved treatment for use in acute ischemic stroke.<sup>76</sup> Importantly, the dosing regimen of alteplase for STEMI and stroke patients differs. The most feared complication of treatment with alteplase in acute stroke is symptomatic

**Table 4. Common Medications Errors in Patients With Ischemic Stroke**

Medication	Type of Error	Reason for Use	Preventable Adverse Event	Guideline Recommendations <sup>74,75</sup>
IV tPA	Underuse; misuse (errors in dosing, patient selection, timing)	Acute stroke treatment	Increased risk of hemorrhagic complications	Administer at the dose of 0.9 mg/kg (maximum 90 mg) within 4.5 hours of onset in patients who qualify for treatment. Rigorous BP control for 24 hours (keep BP <180/105 mm Hg during and after infusion). Avoid anticoagulants and antiplatelet agents within the first 24 hours
Heparin	Overuse; misuse (errors in dosing, monitoring, prescribing, transcribing)	Prevention of early stroke recurrence and stroke progression	Increased risk of hemorrhagic complications	Not recommended, even for those with AF
Warfarin	Underuse; misuse (errors in dosing, monitoring, prescribing)	Primary and secondary stroke prevention in AF	Increased risk of thrombotic and hemorrhagic complications	Commence anticoagulation with adjusted-dose warfarin (target INR 2.0 to 3.0) in patients with ischemic stroke with persistent or paroxysmal AF
Antihypertensive medications	Misuse (excessive BP reduction in the setting of pressure-sensitive stroke)	High BP during the acute period	Possible infarct progression	Lower BP only if >220/120 mm Hg with a goal to reduce by ≈15% during the first 24 hours of stroke, except for organ dysfunction that necessitates rapid reduction and fibrinolytic therapy
Combination antiplatelets (aspirin-clopidogrel combination)	Overuse (unproven indication)	Secondary stroke prevention	Increased risk of hemorrhagic complications	Not recommended unless there is a specific indication (stent procedure or ACS)
Corticosteroids	Misuse (unproven indication)	Brain edema	Increased risk of infection and other steroid-related complications	Not recommended
Mannitol	Misuse (errors in dosing, timing, and patient selection)	Brain edema	Acute renal failure, exacerbation of congestive heart failure, electrolyte imbalance	0.25 to 2 g/kg IV administered over 20 minutes unless there is frank congestive heart failure or renal failure
IV infusion of hypotonic solutions (NaCl 0.45%, glucose 5%)	Misuse (error in dosing)	Hydration, hypoglycemia	Brain edema	Not recommended
Gadolinium-based MR contrast agents	Overuse (error in patient selection)	Contrast MRI	Nephrogenic systemic fibrosis	Carefully weigh the benefits and risks in patients with acute renal failure or chronic kidney disease (GFR <30 mL · min <sup>-1</sup> · 1.73 m <sup>-2</sup> ) or acute renal insufficiency of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period. For patients receiving hemodialysis, consider prompt hemodialysis after administration of the MRI contrast

BP indicates blood pressure; AF, atrial fibrillation; MR, magnetic resonance; MRI, magnetic resonance imaging; and GFR, glomerular filtration rate.

intracranial hemorrhage, which occurs in approximately 5% of patients treated. Strict adherence to protocol guidelines is recommended to reduce the risk of hemorrhagic complications.<sup>75,76</sup> The 2009 updated science advisory has recommended increasing the use of alteplase from 3 hours to 4.5 hours from symptom onset.<sup>77</sup> Guidelines also require careful assessment of clinical conditions that are associated with increased risk for hemorrhagic complications and demand that brain computed tomography, blood testing, and electrocardiography be performed before alteplase therapy is administered. Similar to fibrinolysis for STEMI patients, it is not necessary to withhold alteplase until baseline laboratory testing for thrombocytopenia or coagulopathy is completed if the clinical suspicion for these disorders is low. Because time is a critical determinant of

treatment effectiveness,<sup>78</sup> it is recommended that fibrinolysis be initiated within 60 minutes of hospital admission.<sup>67</sup> This narrow therapeutic window inevitably leads to deviations from protocol guidelines. Early reports of postmarketing experience with intravenous alteplase demonstrate up to a 50% incidence of protocol deviations.<sup>79</sup> More recent studies report lower but still significant rates that range from 14% to 34%.<sup>80,81</sup> Common protocol deviations include start of treatment beyond the approved time window, failure to maintain blood pressure below desired limits during and after treatment, administration of alteplase despite abnormal baseline coagulation tests, and administration of heparin and antiplatelet agents during the first 24 hours after treatment. Less commonly reported medication errors with alteplase include overdose (because

the alteplase dose differs for stroke compared with STEMI patients),<sup>81,82</sup> absence of baseline computed tomography, misinterpretation of computed tomography findings,<sup>82</sup> and medication name confusion.<sup>83</sup> Strict adherence to protocol guidelines is critical, because deviations are associated with a more than 2-fold increase in the risk of symptomatic intracranial hemorrhage.<sup>82,84,85</sup> Once intracranial hemorrhage occurs, the likelihood of functional independence is trivial, and the probability of survival is only 20% to 50%.<sup>80–82</sup>

Intravenous fibrinolysis with alteplase is substantially underused in ischemic stroke. A recent study of 366 194 ischemic stroke admissions to US hospitals between 1999 and 2004 found a treatment rate of only 1%.<sup>86</sup> Other reports also show that only approximately 1% to 2% of patients with ischemic stroke are being treated with alteplase.<sup>81,87,88</sup> The mean annual number of patients treated with alteplase per hospital in the United States is only 3. This limited experience of emergency physicians and nurses with stroke fibrinolytic therapy protocols appears to be an important contributor to the occurrence of errors. The implementation of systems that provide an integrated response by neurologists, emergency physicians, nurses, and emergency medical services personnel could not only diminish this source of error but also increase the use of fibrinolytic agents<sup>89,90</sup> and improve patient care and outcomes.<sup>91</sup>

Despite guidelines issued by the AHA/American Stroke Association on the early management of ischemic stroke stating that urgent anticoagulation with heparin is not recommended for the treatment of patients with acute ischemic stroke,<sup>76</sup> physicians continue to use heparin in a substantial proportion of patients to prevent infarct progression and stroke recurrence.<sup>92,93</sup> There is currently no evidence that indiscriminate use of heparin offers a net benefit in the management of acute ischemic stroke.<sup>94–98</sup> On the contrary, heparin treatment is associated with a high rate of hemorrhage.<sup>73,74</sup> Most errors with heparin administration occur as a result of its unpredictable pharmacokinetics, the need for frequent laboratory testing and dose changes, and prolonged continuous infusion. A weight-based nomogram developed for the use of heparin in stroke also appears to reduce the need for frequent dose adjustments and hemorrhagic complications.<sup>99</sup>

In contrast to heparin, anticoagulation with warfarin is substantially underused for both primary and secondary prevention of stroke in patients with nonvalvular atrial fibrillation.<sup>75,76</sup> Several studies have shown that only approximately 50% of patients with nonvalvular atrial fibrillation who have no clinically significant contraindication to anticoagulation receive warfarin.<sup>100–102</sup> Because the therapeutic window of warfarin is narrow and its pharmacokinetics are poorly predictable, the therapeutic range is achieved only 60% of time.<sup>103</sup> Both subtherapeutic and supratherapeutic international normalized ratios are associated with a higher frequency of adverse events (thrombosis and hemorrhage).<sup>104</sup> Advanced age, changes in diet, comorbid conditions, and use of multiple medications that interfere with absorption and metabolism of

warfarin appear to be associated with deviations from the optimal international normalized ratio target.<sup>105</sup> There are several anecdotal reports showing that temporary withdrawal of warfarin in patients requiring an invasive procedure (eg, dental extraction, skin biopsy) is associated with occurrence of ischemic stroke.<sup>106,107</sup> A statement issued by the American College of Chest Physicians recommends the use of bridging therapy with heparin or low-molecular-weight heparin during temporary withdrawal in selected patients undergoing invasive procedures.<sup>97</sup> Participation in the AHA's Get With The Guidelines–Stroke<sup>108</sup> and the Stroke PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment)<sup>109</sup> quality improvement programs is associated with improved adherence to warfarin therapy for the secondary prevention of stroke in patients with atrial fibrillation.

### Methods to Limit Medication Errors

The recent Institute of Medicine report<sup>4</sup> included recommendations to improve patient outcomes by minimizing medication errors. The Agency for Healthcare Research and Quality has published evidence-based recommendations.<sup>110</sup> In addition, the National Quality Forum,<sup>111</sup> The Joint Commission,<sup>112</sup> the Institute for Safe Medication Practices,<sup>113</sup> the National Coordinating Council for Medication Error Reporting and Prevention,<sup>114</sup> the Institute for Healthcare Improvement,<sup>115</sup> and the American Society of Health-System Pharmacists<sup>116</sup> are among the most widely recognized organizations that have published strategies to prevent medication errors.

Important steps are being taken to begin the process of identification and reporting of medical errors in the ED. Identification of the occurrence of medical errors, followed by voluntary provider reporting, is critical.<sup>117–119</sup> Common definitions of medication error and a blame-free culture that encourages the reporting of errors in the ED can potentially improve care through early recognition of inappropriate treatment.<sup>120</sup>

The National Emergency Department Safety Study is being implemented currently in 85 EDs across the United States affiliated with the Emergency Medicine Network (EMNet).<sup>121</sup> The purpose of this safety study is to identify, characterize, and confirm medication errors for conditions such as STEMI. Studies such as this can identify sources for error, and equally importantly, they can begin to develop a culture for disclosing medication errors in the ED. Because the ED is a complex, high-pressure, high-risk, and sometimes chaotic environment with multiple care providers interacting to deliver medications to critically ill and injured patients, a culture of open communication must exist such that medication errors are identified and disclosed as early as possible after occurrence.

There are 4 points in the medication use process at which errors may occur: (1) The medication is ordered (written, electronic, or oral), (2) the medication order is transcribed and verified, (3) the medication is dispensed, and (4) the medication is administered. There are important interventions related to each of these 4 medication-use

processes. A cardiovascular pharmacy and therapeutics subcommittee of the larger hospital-based safety committee can focus on managing the cardiovascular medication formulary to increase safety, implement unit dosing, create policies and procedures to ensure compliance with ordering processes, limit verbal orders, ban specific abbreviations and symbols, and develop protocols for high-risk medications.

Medication reconciliation is an important component to reduce medication errors. There are numerous patient handoffs from admission to transfer from the ED, transfers across inpatient units, transfers to procedure suites and operating rooms, and at discharge. In particular, medication discrepancies commonly occur at hospital discharge and are associated with an increased risk of adverse medication events.<sup>122,123</sup> Reconciliation is feasible when medication data are transmitted electronically among providers, with patient confirmation. The following 3 steps are required: First, an accurate and complete medication and allergy list must be compiled. Second, the data must be structured into components, including medication name, dose, route, frequency, duration, and start date. Third, these data must be formatted to allow disparate computer systems to understand both their content and structure.

Most organizations recommend implementation of technological interventions, including computerized provider order entry (CPOE) with clinical decision support and bedside bar coding. Other specific interventions with broad support include implementation and utilization of unit dosing, programmable infusion pumps with flow protection, inclusion of clinical pharmacists in patient rounds, standardization of prescription writing and elimination of certain abbreviations, utilization of written protocols for high-risk medications, and standardization and limiting of verbal medication orders. Additional general recommendations include the adoption of a systems-oriented approach to medication errors, the creation of a culture of safety, and improvements in medication error identification and reporting.

In a 2007 survey, 10% of all hospitals and 26% of hospitals with more than 400 beds had CPOE with clinical decision support.<sup>124,125</sup> In an analysis of 10 studies that evaluated CPOE with clinical decision support, rates of medication errors were reduced by 13% to 86%, and rates of preventable adverse medication events were reduced by 17% to 62%.<sup>4</sup> Dosing guidance, medication-allergy checking, and duplicate-therapy checking are standard mechanisms to reduce common prescribing errors.<sup>126</sup> Advanced dosing-decision support, which takes into account the patient's age, renal function, hepatic function, weight, height, and fluid status, offers additional medication safety features.

Although CPOE with clinical decision support has the potential to deliver benefits, it is clear that computer systems can introduce errors and potentially worsen outcomes in some instances.<sup>127,128</sup> There may be unintended consequences if healthcare providers do not carefully plan and implement major clinical transformations such as CPOE.<sup>129</sup> Continuous monitoring for problems during and

after implementation, along with rapid system improvements, is critical.

### Role of the Healthcare Team

The process of administering a medication to a hospitalized patient requires many steps and is multidisciplinary. The involvement of attending physicians, physicians-in-training, pharmacists, and nurses as key members of the inpatient healthcare team is critical to minimizing medication errors in patients with acute cardiovascular disease. Good communication is critical as patients transition between the ambulance, ED, intensive care unit, telemetry floor, and outpatient environments to ensure that appropriate dose adjustments and monitoring occur. Physicians-in-training frequently transfer care to on-call teams, which creates another opportunity for medication error in these handoffs. Adverse medication events occur most frequently on the day of admission, in the early morning hours, and during nursing shift changes.<sup>130</sup> The timing of errors emphasizes the importance of effective transitions of care.

Nurses are taught the most important step to ensure safety with respect to administering medications is to check the 5 rights: Right medication, right dose, right time, right patient, and right route. Safety reporting involves the collection, analysis, and dissemination of information on errors, which positively influences patient safety. Root cause analysis and failure mode and effects analysis are 2 multidisciplinary strategies that are often used to examine medication errors. Failure mode and effects analysis is a prospective process, whereas the root cause analysis is reactive in that it occurs after the error and harm. Root cause analyses have resulted in nursing practice changes, including labeling of the infusion pump and the intravenous tubing distally and verification of infusion pumps and associated infusions by 2 nurses at change of shift and whenever new infusions are initiated or the medication concentration is changed. Standardized medication concentrations, either premixed or mixed by the pharmacy, have been found to be helpful in decreasing the number of medication errors.

Smart infusion pumps, bar coding, and personal digital assistant technology are rapidly entering the acute care setting and have been found to be associated with a reduction in medication errors.<sup>131,132</sup> The use of software in a World Wide Web-based intranet that allows the nurse to report a medication error has been found to support this type of culture.<sup>133</sup>

Pharmacist involvement in interdisciplinary cardiovascular or intensive care unit patient-care rounds has been found to increase identification and tracking of medication errors<sup>134,135</sup> and reduce the rate of adverse medication events caused by prescribing errors.<sup>136</sup> Hospitals with pharmacist-provided heparin-management services are reported to have lower mortality ( $P<0.0001$ ), shorter length of stay ( $P<0.0001$ ), lower Medicare charges ( $P<0.0001$ ), and lower rates of bleeding complications ( $P<0.0009$ ) than hospitals without such services.<sup>137</sup>

The ratio of clinical pharmacists to patient beds was associated with a lower hospital mortality rate in an analysis

of data from the American Hospital Association’s Annual Survey of Hospitals and National Clinical Pharmacy Services database of more than 2.5 million patients in 885 hospitals.<sup>138</sup> Pharmacists are integral members of the rapid-response team.<sup>139</sup> Pharmacist participation in the hospital cardiopulmonary resuscitation team was associated with a reduction in hospital mortality rate.<sup>140</sup> Pharmacist-led educational in-service training sessions were found to be an effective way to reduce excess dosing of eptifibatid in patients with renal dysfunction (53% versus 31%,  $P < 0.001$ ).<sup>141</sup> Pharmacist participation on cardiac care unit and inpatient teams improves the safety of patients at risk for medication errors. Improved prescribing of angiotensin-converting enzyme inhibitors (90% versus 84%,  $P = 0.02$ ) and statins (94% versus 89%,  $P = 0.02$ ) was observed when pharmacists were alerted to patients with myocardial infarction through computer alerts for positive troponin values. Pharmacists’ review of medications ordered in EDs also has been associated with a reduction in medication errors.<sup>142</sup>

Strategies to improve the safety of high-alert medications include development of a standardized approach to prescribing these medications for common indications through protocols, critical pathways, and preprinted order forms or computerized order sets. The variability in available strengths of parenteral agents also should be minimized.

**Reporting of Adverse Medication Errors**

Detection, reporting, and analysis of medication errors are essential to ensure patient safety. According to the Institute for Safe Medication Practices, self-reporting strategies remain the most common method for identification of medication errors; however, it is likely that only a minority of medication errors are actually reported. In a prospective single-center study, only 92 (13%) of 731 adverse medication events were detected by physician, pharmacist, and nurse voluntary reporting.<sup>143</sup> The remaining 87% of events were detected with a computerized adverse medication event monitoring system. Computerized adverse medication event surveillance systems detect events at much higher rates than voluntary reporting, and the difference may be greater in community than in academic hospital settings.<sup>144</sup> Compared with chart review, computerized adverse medication event monitoring systems have fair sensitivity (45% to 79%) but poor positive predictive value (11% to 21%), which suggests that the accuracy of computer-based systems still needs improvement.<sup>145,146</sup> The ability to improve reporting systems to detect medication errors is complicated by a litigation system that encourages secrecy. In order for improvements to be made, errors must be reported and analyzed; liability reform must be a component of the overall solution to the problem of medication errors to enable process improvement without fear.<sup>147,148</sup>

**Conclusions**

Despite being in the national spotlight for most of the past decade, medication errors that affect the management of patients with acute cardiovascular disease continue to be a

**Table 5. Recommendations for Medication Safety in Acute Cardiovascular Care**

Recommendation	Class (Level of Evidence)
1. An accurate weight should be obtained on admission	I (C)
2. Estimated creatinine clearance should be calculated with the Cockcroft-Gault formula on admission and as changes in creatinine occur	I (B)
3. Because of age-related changes in pharmacokinetics, pharmacodynamics, and renal function, medication dosage adjustments and heightened surveillance for adverse medication events are recommended	I (B)
4. Order forms and protocols for anticoagulation should be standardized	I (B)
5. Pharmacists and nurses should be integrated within the cardiovascular care teams in the ED, ICU, and inpatient wards to enhance communication and medication safety	I (B)
6. CPOE, medication bar-coding technology, and smart infusion pumps should be implemented throughout all inpatient wards, including the ED	I (B)
7. Staff should be educated on high-alert medications (particularly anticoagulants), safe medication administration techniques, medication reconciliation procedures, look-alike/sound-alike medications, and automated dispensing device technologies	I (C)
8. An organizational culture of safety that promotes no-fault internal and external medication error reporting and interdisciplinary quality improvement review processes to reduce the frequency and impact of medication errors is recommended	I (C)

ICU indicates intensive care unit.

common and costly problem. Table 5 summarizes the major findings and recommendations from the present scientific statement. Both medication errors of omission and commission constitute important errors in patients with acute cardiovascular illness. In the aging population, numerous medications are prescribed; age-related changes in pharmacokinetics, pharmacodynamics, and renal function require dose adjustments and vigilant surveillance for adverse medication events. Because numerous cardiovascular medications are dosed on the basis of renal function, it is critical to calculate the eCrCl with the Cockcroft-Gault formula on admission for every patient and as changes in body weight and serum creatinine occur. To reduce medication error incidence and its impact, it is critical to integrate nurses and pharmacists into the cardiovascular healthcare team in the ED, intensive care unit, catheterization laboratories, operating rooms, and inpatient wards.

With increasing patient age and the frequent prescribing of multiple medications to acutely ill patients, concerted

efforts for the prevention, reporting, and management of medication errors must be made nationally. Public reporting of hospital compliance with myocardial infarction and heart failure performance measures has heightened public awareness of medication errors. The current methods for generating and examining information about medication errors are inadequate and limit our understanding of accurate incidence rates and costs of these errors, as well as the efficacy of prevention strategies. The adoption of a number of technologies, including CPOE with clinical decision support, bar coding, and smart infusion-pump technology, is required, particularly in cardiovascular patients treated with high-risk medications such as anticoagulants. These systems are costly to develop and maintain and will require the coordinated support of payers, healthcare providers, insurers, and employers to fund the necessary solutions to avoid medication errors and their consequences.

Key changes in oversight, regulation, and payment are needed to promote improved medication error reporting by all stakeholders, develop minimum functionality standards for error-prevention technologies, and enhance education of healthcare professionals early in their training and throughout their careers to ensure safe medication-management practices. No comprehensive national monitoring system exists for patient safety and medication errors. The Agency for Healthcare Research and Quality has been tasked to set explicit, quantitative, and ambitious goals for patient safety with measurable end points by 2010.<sup>149</sup> To reduce the frequency and clinical impact of medication errors, the medical community must work collectively with The Joint Commission, the National Quality Forum, the American Hospital Association, the American Medical Association, the Leapfrog Group, and all major payers, including the Centers for Medicare and Medicaid Services, to engage patients and caregivers in becoming active partners in safe medication practices, improve and standardize error-detection rates, and implement safer methods to prescribe, dispense, and track medications.

## Appendix

### Electronic Links to Related Online Resources

Electronic Link	Resource
<b>Medication error reporting</b>	
<a href="http://www.ismp.org">www.ismp.org</a>	Institute for Safe Medication Practices Medication Errors Reporting System (MERP)
<a href="http://www.nccmerp.org">www.nccmerp.org</a>	National Coordinating Council for Medication Error Reporting and Prevention
<a href="http://www.usp.org/hqi/patientSafety/medmarx">www.usp.org/hqi/patientSafety/medmarx</a>	US Pharmacopeia's MEDMARX, a national, Internet-accessible database that hospitals and healthcare systems use to track and trend adverse medication reactions and medication errors. Telephone 800-23-ERROR (800-233-7767)
<a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a>	US Food and Drug Administration's Safety Information and Adverse Event Reporting Program. Telephone 800-FDA-1088
<b>Additional online sources for medication error information</b>	
<a href="http://www.ahrq.gov">www.ahrq.gov</a>	Agency for Healthcare Research and Quality
<a href="http://www.pharmacist.com">www.pharmacist.com</a>	American Pharmacists Association
<a href="http://www.ashp.org">www.ashp.org</a>	American Society of Health-System Pharmacists
<a href="http://www.cihsp.org">www.cihsp.org</a>	California Institute for Health Systems Performance (medication safety section has model plan for medication error reduction)
<a href="http://www.icsi.org">www.icsi.org</a>	Institute for Clinical Systems Improvement
<a href="http://www.ihl.org">www.ihl.org</a>	Institute for Healthcare Improvement
<a href="http://www.jointcommission.org">www.jointcommission.org</a>	The Joint Commission
<a href="http://www.medpathways.info">www.medpathways.info</a>	Pathways for Medication Safety (tools for reducing medication errors)

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Andrew D. Michaels	University of Utah	Abbott Laboratories†; Cytokinetics†; Inovise Medical†	None	Daiichi Sankyo/Eli Lilly*	None	None	Boston Scientific*; Medicare*	None
Karen P. Alexander	Duke University	None	None	None	None	None	None	None
Hakan Ay	Massachusetts General Hospital	NIH*	None	None	None	None	None	None
W. Brian Gibler	University of Cincinnati	Abbott Point of Care (i-STAT)†; Bristol-Myers Squibb†; Sanofi-Aventis†; Schering-Plough†	None	None	None	Inovise*; Matryx Group*; Saloam*	ArgiNOx*; Astellas*; AstraZeneca*; Daiichi Sankyo/Lilly*; HeartScape Technologies*; Sanofi-Aventis/Bristol-Myers Squibb*; Schering-Plough*	Unrestricted educational grant support to EMCREG International from Abbott Point of Care (i-STAT)†; ArgiNOx†; Biosite†; Bristol-Myers Squibb†; Daiichi Sankyo/Lilly†; Inovise†; The Medicines Company†; Millennium Pharmaceuticals†; PDL BioPharma†; Roche Diagnostics†; Sanofi-Aventis†; Schering-Plough†
Barbara Leeper	Baylor Medical Center	None	None	None	None	None	None	None
L. Kristin Newby	Duke University Medical Center	AstraZeneca*; BG Medicine*; GlaxoSmithKline†; Inverness Medical*; Medicare†; NHLBI†; Schering-Plough†	diaDexus†	Schering-Plough*; theHeart.org*	None	None	Biosite*; Novartis*; Roche Diagnostics*	None
E. Magnus Ohman	Duke University	Berlex*; Bristol-Myers Squibb*; Eli Lilly*; Millennium Pharmaceuticals*; Sanofi-Aventis*; Schering-Plough*; The Medicines Company*	None	Gilead Sciences (formerly CV Therapeutics)*; The Medicines Company*	None	Inovise*; Medtronic*; Savacor*	Abiomed*; Datascope*; Gilead Sciences (formerly CV Therapeutics)*; Inovise*; LipoScience*; NorthPoint Domain*; Pozen*; Response Biomedical*; Savacor*; The Medicines Company*; WebMD*	None
Sarah A. Spinler	University of the Sciences in Philadelphia	None	None	Bristol-Myers Squibb*; GlaxoSmithKline*; Sanofi-Aventis*	None	None	Sanofi-Aventis*	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Joseph S. Alpert	University of Arizona	None	None	None	None	None	Sanofi-Aventis*	None
Savitri Fedson	University of Chicago	None	None	None	None	None	None	None
Gregg C. Fonarow	University of California Los Angeles Medical Center	NHLBI†	None	GlaxoSmithKline†; Merck/Schering-Plough†; Medtronic†; Pfizer†; Bristol-Myers Squibb/Sanofi†; Abbott†; AstraZeneca*	None	None	GlaxoSmithKline*; Novartis†; Medtronic†; Merck/Schering-Plough*; Forrest*	None
Pooja Khatri	University of Cincinnati	NIH K23†	None	None	None	None	None	None
Janet Parkosewich	Yale University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## References

- Kohn LT, Corrigan JM, Donaldson MS, eds; for the Committee on Quality of Health Care in America, Institute of Medicine. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 2000.
- Hayward RA, Hofer TP. Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *JAMA*. 2001;286:415–420.
- Health Grades Inc. *Patient Safety in American Hospitals*. Golden, Colo: Health Grades Inc; 2004.
- Aspden P, Wolcott J, Bootman JL, Cronenwelt LR, eds; for the Committee on Identifying and Preventing Medication Errors, Institute of Medicine. *Preventing Medication Errors*. Washington, DC: National Academy Press; 2006.
- Freedman JE, Becker RC, Adams JE, Borzak S, Jesse RL, Newby LK, O'Gara P, Pezzullo JC, Kerber R, Coleman B, Broderick J, Yasuda S, Cannon C. Medication errors in acute cardiac care: an American Heart Association Scientific Statement from the Council on Clinical Cardiology Subcommittee on Acute Cardiac Care, Council on Cardiopulmonary and Critical Care, Council on Cardiovascular Nursing, and Council on Stroke. *Circulation*. 2002;106:2623–2629.
- National Coordination Council for Medication Error Reporting and Prevention Web site. Available at: <http://www.nccmerp.org/aboutMedErrors.html>. Accessed February 9, 2010.
- Hicks RW, Becker SC, Cousins DD, eds. *MEDMARX Data Report: A Report on the Relationship of Drug Names and Medication Errors in Response to the Institute of Medicine's Call to Action (2003–2006 Findings and Trends 2002–2006)*. Rockville, Md: Center for the Advancement of Patient Safety, US Pharmacopeia; 2008.
- Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W; on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1047–1060.
- 5 Million Lives Campaign. *Getting Started Kit: Prevent Harm From High-Alert Medications*. Cambridge, Mass: Institute for Healthcare Improvement; 2008. Available at: <http://www.ihl.org>. Accessed December 1, 2009.
- Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, Pirmohamed M. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol*. 2007;63:136–147.
- Kanjanarat P, Winterstein AG, John TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm*. 2003;60:1750–1759.
- Gibson CM, Pride YB, Frederick PD, Pollack CV Jr, Canto JG, Tiefenbrunn AJ, Weaver WD, Lambrew CT, French WJ, Peterson ED, Rogers WJ. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156:1035–1044.
- Lee HY, Cooke CE, Robertson TA. Use of secondary prevention drug therapy in patients with acute coronary syndrome after hospital discharge. *J Manag Care Pharm*. 2008;14:271–280.
- Mehta RH, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Brindis RG, Smith SC Jr, Harrington RA, Fintel D, Fraulo ES, Califf RM, Gibler WB, Ohman EM, Peterson ED. Recent trends in the care of patients with non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE initiative. *Arch Intern Med*. 2006;166:2027–2034.
- Michaels AD, Maynard C, Every NR, Barron HV; National Registry of Myocardial Infarction 2 Participants. Early use of ACE inhibitors in the treatment of acute myocardial infarction in the United States: experience from the National Registry of Myocardial Infarction 2. *Am J Cardiol*. 1999;84:1176–1181.
- Murphy SA, Cannon CP, Wiviott SD, de Lemos JA, Blazing MA, McCabe CH, Califf RM, Braunwald E. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). *Am J Cardiol*. 2007;100:1047–1051.
- Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Summary: 2005 emergency department summary. *Adv Data*. June 29, 2007;1–32.
- Diercks DB, Roe MT, Chen AY, Peacock WF, Kirk JD, Pollack CV Jr, Gibler WB, Smith SC Jr, Ohman M, Peterson ED. Prolonged emergency department stays of non-ST-segment-elevation myocardial infarction patients are associated with worse adherence to the American College of Cardiology/American Heart Association guidelines for management and increased adverse events. *Ann Emerg Med*. 2007;50:489–496.



19. Mehta RH, Newby LK, Patel Y, Hoekstra JW, Miller CD, Chen AY, Lytle BL, Diercks DB, Summers RL, Brogan GX, Peacock WF, Pollack CV Jr, Roe MT, Peterson ED, Ohman EM, Gibler WB; CRUSADE Investigators. The impact of emergency department structure and care processes in delivering care for non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2006;152:648–660.
20. Campbell SG, Croskerry P, Bond WF. Profiles in patient safety: a “perfect storm” in the emergency department. *Acad Emerg Med*. 2007;14:743–749.
21. Zaidenstein R, Eyal S, Efrati S, Akivison L, Michowitz MK, Nagornov V, Golik A. Adverse drug events in hospitalized patients treated with cardiovascular medications and anticoagulants. *Pharmacoepidemiol Drug Saf*. 2002;11:235–238.
22. Ellerbeck EF, Jencks SF, Radford MJ, Kresowik TF, Craig AS, Gold JA, Krumholz HM, Vogel RA. Quality of care for Medicare patients with acute myocardial infarction: a four-state pilot study from the Cooperative Cardiovascular Project. *JAMA*. 1995;273:1509–1514.
23. Alexander KP, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Foody JM, Boden WE, Smith SC Jr, Gibler WB, Ohman EM, Peterson ED; CRUSADE Investigators. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005;46:1479–1487.
24. Flanagan PS, MacKinnon NJ, Bowles SK, Kirkland SA. Validation of four clinical indicators of preventable drug-related morbidity. *Ann Pharmacother*. 2004;38:20–24.
25. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. *BMJ*. 2000;320:741–744.
26. Picone DM, Titler MG, Dochterman J, Shever L, Kim T, Abramowitz P, Kanak M, Qin R. Predictors of medication errors among elderly hospitalized patients. *Am J Med Qual*. 2008;23:115–127.
27. Simon SR, Andrade SE, Ellis JL, Nelson WW, Gurwitz JH, Lafata JE, Davis RL, Feldstein A, Raebel MA. Baseline laboratory monitoring of cardiovascular medications in elderly health maintenance organization enrollees. *J Am Geriatr Soc*. 2005;53:2165–2169.
28. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes [published correction appears in *JAMA*. 2006;295:628]. *JAMA*. 2005;294:3108–3116.
29. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
30. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461–470.
31. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *Circulation*. 2007;116:e148–e304.
32. Melloni C, Peterson ED, Chen AY, Szczech LA, Newby LK, Harrington RA, Gibler WB, Ohman EM, Spinler SA, Roe MT, Alexander KP. Cockcroft-Gault versus Modification of Diet in Renal Disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2008;51:991–996.
33. GFR calculator. National Kidney Foundation Web site. Available at: <http://www.kidney.org/professionals/KLS/GFR.cfm>. Accessed December 1, 2009.
34. CKD and drug dosing: information for providers: estimation of kidney function for prescription medication dosage in adults. National Kidney Disease Education Program Web site. Available at: <http://www.nkdep.nih.gov/professionals/drug-dosing-information.htm>. Accessed December 1, 2009.
35. Galanter WL, Didomenico RJ, Polikaitis A. A trial of automated decision support alerts for contraindicated medications using computerized physician order entry. *J Am Med Inform Assoc*. 2005;12:269–274.
36. Reddan D, Laville M, Garovic VD. Contrast-induced nephropathy and its prevention: what do we really know from evidence-based findings? *J Nephrol*. 2009;22:333–351.
37. US Food and Drug Administration. Information for healthcare professionals: Gadolinium-based contrast agents for magnetic resonance imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm>. Last update August 13, 2009. Accessed December 1, 2009.
38. Anglemyer BL, Hernandez C, Brice H, Zou B. The accuracy of visual estimation of body weight in the ED. *Am J Emerg Med*. 2004;22:526–529.
39. Menon S, Kelly AM. How accurate is weight estimation in the emergency department? *Emerg Med Australas*. 2005;17:113–116.
40. Martin DR, Soria DM, Brown CG, Pepe PE, Gonzalez E, Jastremski M, Stueven H, Cummins RO. Agreement between paramedic-estimated weights and subsequent hospital measurements in adults with out-of-hospital cardiac arrest. *Prehosp Disaster Med*. 1994;9:54–56.
41. Araghi A, Bander JJ, Guzman JA. Arterial blood pressure monitoring in overweight critically ill patients: invasive or noninvasive? *Crit Care*. 2006;10:R64.
42. Rogers WJ, Bowlby LJ, Chandra NC, French WJ, Gore JM, Lambrew CT, Rubison RM, Tiefenbrunn AJ, Weaver WD. Treatment of myocardial infarction in the United States (1990 to 1993): observations from the National Registry of Myocardial Infarction. *Circulation*. 1994;90:2103–2114.
43. Mehta RH, Montoye CK, Faul J, Nagle DJ, Kure J, Raj E, Fattal P, Sharrif S, Amlani M, Changezi HU, Skorc S, Bailey N, Bourque T, LaTarte M, McLean D, Savoy S, Werner P, Baker PL, DeFranco A, Eagle KA; American College of Cardiology Guidelines Applied in Practice Steering Committee. Enhancing quality of care for acute myocardial infarction: shifting the focus of improvement from key indicators to process of care and tool use: the American College of Cardiology Acute Myocardial Infarction Guidelines Applied in Practice Project in Michigan: Flint and Saginaw Expansion. *J Am Coll Cardiol*. 2004;43:2166–2173.
44. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120:2271–2306.
45. Krumholz HM, Anderson JL, Bachelder BL, Fesmire FM, Fihn SD, Foody JM, Ho PM, Kosiborod MN, Masoudi FM, Nallamothu BK. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction). *Circulation*. 2008;118:2598–2648.
46. Lewis WR, Peterson ED, Cannon CP, Super DM, LaBresh KA, Quealy K, Liang L, Fonarow GC. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. *Arch Intern Med*. 2008;168:1813–1819.
47. Tickoo S, Roe MT, Peterson ED, Milford-Beland S, Ohman EM, Gibler WB, Pollack CV Jr, Cannon CP; CRUSADE Investigators. Patterns of aspirin dosing in non-ST-elevation acute coronary syndromes in the CRUSADE Quality Improvement Initiative. *Am J Cardiol*. 2007;99:1496–1499.
48. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation*. 2003;108:1682–1687.
49. Berger JS, Stebbins A, Granger CB, Ohman EM, Armstrong PW, Van de Werf F, White HD, Simes RJ, Harrington RA, Califf RM, Peterson ED. Initial aspirin dose and outcome among ST-elevation myocardial

- infarction patients treated with fibrinolytic therapy. *Circulation*. 2008;117:192–199.
50. Mehta SR. A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes: results of the CURRENT OASIS 7 trial. *Eur Heart J*. 2009;30. Abstract.
  51. Ramanuja S, Breall JA, Kalaria VG. Approach to “aspirin allergy” in cardiovascular patients. *Circulation*. 2004;110:e1–e4.
  52. Alexander D, Ou FS, Roe MT, Pollack CV Jr, Ohman EM, Cannon CP, Gibler WB, Fintel DJ, Peterson ED, Brown DL. Use of and in-hospital outcomes after early clopidogrel therapy in patients not undergoing an early invasive strategy for treatment of non-ST-segment elevation myocardial infarction: results from Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE). *Am Heart J*. 2008;156:606–612.
  53. Boersma E, Harrington RA, Moliterno DJ, White H, Thérroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials [published correction appears in *Lancet*. 2002;359:2120]. *Lancet*. 2002;359:189–198.
  54. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, Roe MT, Gibler WB, Ohman EM, Peterson ED; for the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Investigators. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Initiative. *Circulation*. 2006;114:1380–1387.
  55. Cannon CP. Thrombolysis medication errors: benefits of bolus thrombolytic agents. *Am J Cardiol*. 2000;85:17C–22C.
  56. Vorchheimer DA, Baruch L, Thompson TD, Kukin ML. North American vs non-North American streptokinase use in GUSTO-I: impact of protocol deviation on mortality benefit of tPA. *Circulation*. 1997;96(suppl):1-535. Abstract.
  57. Cannon CP. Multimodality reperfusion therapy for acute myocardial infarction. *Am Heart J*. 2000;140:707–716.
  58. Mehta RH, Alexander JH, Van de Werf F, Armstrong PW, Pieper KS, Garg J, Califf RM, Granger CB. Relationship of incorrect dosing of fibrinolytic therapy and clinical outcomes. *JAMA*. 2005;293:1746–1750.
  59. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R, Vander Vliet M, Nemeskal R, Leape LL; ADE Prevention Study Group. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA*. 1995;274:29–34.
  60. Wang TY, Chen AY, Alexander KP, Ohman EM, Gibler WB, Peterson ED, Roe MT. Excess heparin dosing among fibrinolytic-treated patients with ST-segment elevation myocardial infarction. *Am J Med*. 2008;121:805–810.
  61. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition) [published correction appears in *Chest*. 2008;134:892]. *Chest*. 2008;133(suppl):454S–545S.
  62. LaPointe NM, Chen AY, Alexander KP, Roe MT, Pollack CV Jr, Lytle BL, Ohman ME, Gibler BW, Peterson ED. Enoxaparin dosing and associated risk of in-hospital bleeding and death in patients with non ST-segment elevation acute coronary syndromes. *Arch Intern Med*. 2007;167:1539–1544.
  63. 2008 National patient safety goals: hospital. The Joint Commission Web site. Available at: [http://www.jointcommission.org/NR/rdonlyres/82B717D8-B16A-4442-AD00-CE3188C2F00A/0/08\\_HAP\\_NPSGs\\_Master.pdf](http://www.jointcommission.org/NR/rdonlyres/82B717D8-B16A-4442-AD00-CE3188C2F00A/0/08_HAP_NPSGs_Master.pdf). Accessed December 1, 2009.
  64. Paradiso-Hardy FL, Gordon WL, Jackevicius CA, Kertland HR, Pearson GJ, Pickering JL, Poirier L, Semchuk BM, Verret L. The importance of in-hospital statin therapy for patients with acute coronary syndromes. *Pharmacotherapy*. 2003;23:506–513.
  65. MedWatch safety alerts for human medical products. US Food and Drug Administration Web site. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095009.htm>. Accessed December 1, 2009.
  66. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551.
  67. Turkoski BB, Lance BR, Tomsik EA. *Drug Information Handbook for Nursing, 10th Edition*. Hudson, Ohio: Lexi-Comp; 2009.
  68. *Tarascon Pocket Pharmacopoeia 2009: Classic Shirt-Pocket Edition*. Sudbury, Mass: Tarascon Publishing; 2009.
  69. Ponniah A, Shakib S, Doecke CJ, Boyce M, Angley M. Post-discharge medication reviews for patients with heart failure: a pilot study. *Pharm World Sci*. 2008;30:810–815.
  70. Fonarow GC, Yancy CW, Heywood JT; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. *Arch Intern Med*. 2005;165:1469–1477.
  71. Ambardekar AV, Fonarow GC, Hernandez AF, Pan W, Yancy CW, Krantz MJ; Get With the Guidelines Steering Committee and Hospitals. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: findings from Get With The Guidelines-Heart Failure (GWTG-HF). *Am Heart J*. 2009;158:644–652.
  72. Daud-Gallotti R, Dutilh Novaes HM, Lorenzi MC, Eluf-Neto J, Namie Okamura M, Tadeu Velasco I. Adverse events and death in stroke patients admitted to the emergency department of a tertiary university hospital. *Eur J Emerg Med*. 2005;12:63–71.
  73. Holloway RG, Tuttle D, Baird T, Skelton WK. The safety of hospital stroke care. *Neurology*. 2007;68:550–555.
  74. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:577–617.
  75. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published corrections appear in *Stroke*. 2007;38:e38 and *Stroke*. 2007;38:e96]. *Stroke*. 2007;38:1655–1711.
  76. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
  77. del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; on behalf of American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40:2945–2948.
  78. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55:1649–1655.
  79. Katzan JL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP, Qu A, Sila CA. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000;283:1151–1158.
  80. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*. 2000;283:1145–1150.
  81. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ*. 2005;172:1307–1312.
  82. Messé SR, Tanne D, Demchuk AM, Cucchiara BL, Levine SR, Kasner SE; Multicenter rt-PA Stroke Survey Group. Dosing errors may impact

the risk of rt-PA for stroke: the Multicenter rt-PA Acute Stroke Survey. *J Stroke Cerebrovasc Dis.* 2004;13:35–40.

83. Scott PA, Davis LA. Do not substitute: IV thrombolytic selection errors in acute stroke. *Stroke.* 2001;32:580–583.
84. Buchan AM, Barber PA, Newcommon N, Karbalai HG, Demchuk AM, Hoyte KM, Klein GM, Feasby TE. Effectiveness of t-PA in acute ischemic stroke: outcome relates to appropriateness. *Neurology.* 2000;54:679–684.
85. Tanne D, Bates VE, Verro P, Kasner SE, Binder JR, Patel SC, Mansbach HH, Daley S, Schultz LR, Karanjia PN, Scott P, Dayno JM, Vereczkey-Porter K, Benesch C, Book D, Coplin WM, Dulli D, Levine SR; t-PA Stroke Survey Group. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. *Neurology.* 1999;53:424–427.
86. Schumacher HC, Bateman BT, Boden-Albala B, Berman MF, Mohr JP, Sacco RL, Pile-Spellman J. Use of thrombolysis in acute ischemic stroke: analysis of the Nationwide Inpatient Sample 1999 to 2004. *Ann Emerg Med.* 2007;50:99–107.
87. Engelstein E, Margulies J, Jeret JS. Lack of t-PA use for acute ischemic stroke in a community hospital: high incidence of exclusion criteria. *Am J Emerg Med.* 2000;18:257–260.
88. Zweifler RM, Brody ML, Graves GC, U TT, Drinkard R, Cunningham S, Rothrock JF. Intravenous t-PA for acute ischemic stroke: therapeutic yield of a stroke code system. *Neurology.* 1998;50:501–503.
89. Rymer MM, Thurtchley D, Summers D; America Brain and Stroke Institute Stroke Team. Expanded modes of tissue plasminogen activator delivery in a comprehensive stroke center increases regional acute stroke interventions. *Stroke.* 2003;34:e58–e60.
90. Frey JL, Jahnke HK, Goslar PW, Partovi S, Flaster MS. tPA by telephone: extending the benefits of a comprehensive stroke center. *Neurology.* 2005;64:154–156.
91. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev.* October 17, 2007: CD000197.
92. Schmidt WP, Heuschmann P, Taeger D, Henningsen H, Buecker-Nott HJ, Berger K. Determinants of IV heparin treatment in patients with ischemic stroke. *Neurology.* 2004;63:2407–2409.
93. Al-Sadat A, Sunbuli M, Chaturvedi S. Use of intravenous heparin by North American neurologists: do the data matter? *Stroke.* 2002;33:1574–1577.
94. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet.* 1997;349:1569–1581.
95. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA.* 1998;279:1265–1272.
96. Gubitz G, Sandercock P, Counsell C. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2004:CD000024.
97. Diener HC, Ringelstein EB, von Kummer R, Langohr HD, Bewermeyer H, Landgraf H, Hennerici M, Welzel D, Gräve M, Brom J, Weidinger G; Therapy of Patients With Acute Stroke (TOPAS) Investigators. Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the TOPAS trial. *Stroke.* 2001;32:22–29.
98. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Martila R, Olsson J, O'Neill D, Orgogozo J, Ringelstein B, van der Sande J, Turpie AG. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial [published correction appears in *Lancet.* 2001;358:1276]. *Lancet.* 2001;358:702–710.
99. Toth C, Voll C. Validation of a weight-based nomogram for the use of intravenous heparin in transient ischemic attack or stroke. *Stroke.* 2002;33:670–674.
100. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. *Arch Intern Med.* 1996;156:2537–2541.
101. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med.* 1999;131:927–934.
102. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of anti-thrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke.* 2000;31:822–827.
103. Reynolds MW, Fahrback K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest.* 2004;126:1938–1945.
104. White HD, Gruber M, Feys J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med.* 2007;167:239–245.
105. Ansell J, Hirsh J, Dalen J, Bussey H, Anderson D, Poller L, Jacobson A, Deykin D, Matchar D. Managing oral anticoagulant therapy. *Chest.* 2001;119(suppl):22S–38S.
106. Akopov SE, Suzuki S, Fredieu A, Kidwell CS, Saver JL, Cohen SN. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines? *Cerebrovasc Dis.* 2005;19:337–342.
107. Grip L, Blombäck M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. *Eur Heart J.* 1991;12:1225–1233.
108. Lewis WR, Fonarow GC, LaBresh KA, Cannon CP, Pan W, Super DM, Sorof SA, Schwamm LH. Differential use of warfarin for secondary stroke prevention in patients with various types of atrial fibrillation. *Am J Cardiol.* 2009;103:227–231.
109. Ovbiagele B, Saver JL, Fredieu A, Suzuki S, Selco S, Rajajee V, McNair N, Razinia T, Kidwell CS. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. *Stroke.* 2004;35:2879–2883.
110. Shojania K, Duncan B, McDonald K, Wachter RM. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices.* Rockville, Md: Agency for Healthcare Research and Quality; 2001. Evidence Report/Technology Assessment, No. 43. AHRQ publication No. 01-E058.
111. National Quality Forum (NQF). *Safe Practices for Better Healthcare: 2009 Update: A Consensus Report.* Washington, DC: National Quality Forum; 2009.
112. Joint Commission Resources. *Medication Use: A Systems Approach to Reducing Errors, 2nd Edition.* Oak Brook, Ill: Joint Commission Resources; 2008. Item No. MU200.
113. Cohen MR, ed. *Medication Errors, 2nd Edition.* Institute for Safe Medication Practices Web site. Available at: <http://www.ismp.org>. Accessed December 1, 2009.
114. National Coordinating Council for Medication Error Reporting and Prevention: Council Recommendations. [Online]. Available at: <http://www.nccmerp.org/council/Recs.html>. Accessed December 1, 2009.
115. Institute for Healthcare Improvement Web site. Available at: <http://www.ihl.org>. Accessed December 1, 2009.
116. American Society of Health-System Pharmacists. Top-priority actions for preventing adverse drug events in hospitals: recommendations of an expert panel. *Am J Health Syst Pharm.* 1996;53:747–751.
117. Moskop JC, Geiderman JM, Hobgood CD, Larkin GL. Emergency physicians and disclosure of medical errors. *Ann Emerg Med.* 2006;48:523–531.
118. Francis RC, Spies CD, Kerner T. Quality management and benchmarking in emergency medicine. *Curr Opin Anaesthesiol.* 2008;21:233–239.
119. Kram R. Critical incident reporting system in emergency medicine. *Curr Opin Anaesthesiol.* 2008;21:240–244.
120. Hobgood C, Weiner B, Tamayo-Sarver JH. Medical error identification, disclosure, and reporting: do emergency medicine provider groups differ? *Acad Emerg Med.* 2006;13:443–451.
121. Sullivan AF, Camargo CA Jr, Cleary PD, Gordon JA, Guadagnoli E, Kaushal R, Magid DJ, Rao SR, Blumenthal D. The National Emergency Department Safety Study: study rationale and design. *Acad Emerg Med.* 2007;14:1182–1189.
122. Wong JD, Bajcar JM, Wong GG, Alibhai SM, Huh JH, Cesta A, Pond GR, Fernandes OA. Medication reconciliation at hospital discharge: evaluating discrepancies. *Ann Pharmacother.* 2008;42:1373–1379.
123. Tjia J, Bonner A, Briesacher BA, McGee S, Terrill E, Miller K. Medication discrepancies upon hospital to skilled nursing facility transitions. *J Gen Intern Med.* 2009;24:630–635.
124. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: prescribing and transcribing—2007. *Am J Health Syst Pharm.* 2008;65:827–843.
125. Pedersen CA, Gumpfer KF. ASHP national survey on informatics: assessment of the adoption and use of pharmacy informatics in U.S. hospitals—2007. *Am J Health Syst Pharm.* 2008;65:2244–2264.
126. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, Classen DC, Bates DW. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Assoc.* 2007;14:29–40.

127. Han YY, Carcillo JA, Venkataraman ST, Clark RS, Watson RS, Nguyen TC, Bayir H, Orr RA. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system [published correction appears in *Pediatrics*. 2006;117:594]. *Pediatrics*. 2005;116:1506–1512.
128. McDonald CJ, Overhage JM, Mamlin BW, Dexter PD, Tierney WM. Physicians, information technology, and health care systems: a journey, not a destination. *J Am Med Inform Assoc*. 2004;11:121–124.
129. Ash JS, Berg M, Coiera E. Some unintended consequences of information technology in health care: the nature of patient care information system-related errors. *J Am Med Inform Assoc*. 2004;11:104–112.
130. Fanikos J, Cina JL, Baroletti S, Fiumara K, Matta L, Goldhaber SZ. Adverse drug events in hospitalized cardiac patients. *Am J Cardiol*. 2007;100:1465–1469.
131. Wolf ZR. Pursuing safe medication use and the promise of technology. *Medsurg Nurs*. 2007;16:92–100.
132. Greenfield S. Medication error reduction and the use of PDA technology. *J Nurs Educ*. 2007;46:127–131.
133. Dixon JF. Going paperless with custom-built Web-based patient occurrence reporting. *Jt Comm J Qual Improv*. 2002;28:387–395.
134. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. *Pharmacoepidemiol Drug Saf*. 2007;16:1129–1135.
135. LaPointe NM, Jollis JG. Medication errors in hospitalized cardiovascular patients. *Arch Intern Med*. 2006;163:1461–1466.
136. Leape LL, Cullen DJ, Clapp MD, Brudick E, Demonaco HJ, Erickson JI, Bates DW. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit [published correction appears in *JAMA*. 2000;283:1293]. *JAMA*. 1999;282:267–270.
137. Bond CA, Raehl CL. Pharmacist-provided anticoagulation management in United States hospitals: death rates, length of stay, Medicare charges, bleeding complications, and transfusions. *Pharmacotherapy*. 2004;24:953–963.
138. Bond CA, Raehl R. Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. *Pharmacotherapy*. 2007;27:481–493.
139. Cooper BE. Pharmacist involvement in a rapid-response team at a community hospital. *Am J Health Syst Pharm*. 2007;64:694–698.
140. Bond CA, Raehl CL, Franke T. Interrelationships among mortality rates, drug costs, total costs of care, and length of stay in United States hospitals: summary and recommendations for clinical pharmacy services and staffing. *Pharmacotherapy*. 2001;21:129–141.
141. Donovan JL, Schroeder WS, Tran MT, Foster K, Forrest A, Lee TB, Gandhi PJ. Assessment of eptifibatide dosing in renal impairment before and after in-service education provided by pharmacists. *J Manag Care Pharm*. 2007;13:598–606.
142. Vasileff HM, Whitten LE, Pink JA, Goldworthy SJ, Angley MT. The effect of medication errors of pharmacists charting medication in an emergency department. *Pharm World Sci*. 2009;31:373–379.
143. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients [published correction appears in *JAMA*. 1992;267:1922]. *JAMA*. 1991;266:2847–2851.
144. Kilbridge PM, Campbell UC, Cozart HB, Mojarad MG. Automated surveillance for adverse drug events at a community hospital and an academic medical center. *J Am Med Inform Assoc*. 2006;13:372–377.
145. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vander Vliet M, Bates DW. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc*. 1998;5:305–314.
146. Hwang SH, Lee S, Koo HK, Kim Y. Evaluation of a computer-based adverse-drug-event monitor. *Am J Health Syst Pharm*. 2008;65:2265–2272.
147. Brennan TA. The Institute of Medicine report on medical errors: could it do harm? *N Engl J Med*. 2000;342:1123–1125.
148. Dekker SW. Criminalization of medical error: who draws the line? *ANZ J Surg*. 2007;77:831–837.
149. Leape LL, Berwick DM. Five years after *To Err is Human*: what have we learned? *JAMA*. 2005;293:2384–2390.

---

KEY WORDS: AHA Scientific Statements ■ acute coronary syndrome ■ anticoagulants ■ medication error ■ patient care ■ patient safety ■ prevention ■ stroke