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STATE-OF-THE-ART PAPER

Drug–Drug Interactions in Cardiovascular Catheterizations and Interventions

CME

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CME Objective for This Article: After reading this article, the reader should understand: 1) The potential for drug-drug interactions among patients undergoing invasive cardiovascular procedures as well as the primary mechanism: altered pharmacokinetics or altered pharmacodynamics. 2) The mechanism to evaluate the likelihood that a drug interaction is actual and meaningful should be appreciated. 3) The leading drugs potentially at risk for altered activity and how these might affect procedural or long-term outcome such as increased risk for thrombosis or hemorrhage.

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Drug–Drug Interactions in Cardiovascular Catheterizations and Interventions

Patients presenting for invasive cardiovascular procedures are frequently taking a variety of medications aimed to treat risk factors related to heart and vascular disease. During the procedure, antithrombotic, sedative, and analgesic medications are commonly needed, and after interventional procedures, new medications are often added for primary and secondary prevention of ischemic events. In addition to these prescribed medications, the use of over-the-counter drugs and supplements continues to rise. Most elderly patients, for example, are taking 5 or more prescribed medications and 1 or more supplements, and they often have some degree of renal insufficiency. This polypharmacy might result in drug–drug interactions that affect the balance of thrombotic and bleeding events during the procedure and during long-term treatment. Mixing of anticoagulants, for instance, might lead to periprocedural bleeding, and this is associated with an increase in long-term adverse events. Furthermore, the range of possible interactions with thienopyridine antiplatelets is of concern, because these drugs are essential to immediate and extended interventional success. The practical challenges in the field are great—some drug–drug interactions are likely present yet not well understood due to limited assays, whereas other interactions have well-described biological effects but seem to be more theoretical, because there is little to no clinical impact. Interventional providers need to be attentive to the potential for drug–drug interaction, the associated harm, and the appropriate action, if any, to minimize the potential for medication-related adverse events. This review will focus on drug–drug interactions that have the potential to affect procedural success, either through increases in immediate complications or compromising longer-term outcome. (J Am Coll Cardiol Intv 2012;5:1195–208)

Polypharmacy is commonplace: over 80% of elderly patients, for example, take at least 1 prescribed medication, and over one-half take 5 or more prescription drugs together (1). This has important implications in the setting of percutaneous coronary intervention (PCI) because drug–drug interactions (DDI) might affect the balance of preventing periprocedural thrombotic events such as myocardial infarction versus the potential for increasing bleeding. Drug–drug interactions can primarily be classified as either pharmacokinetic (where 1 drug affects the absorption, distribution, metabolism, or elimination processes of another) or pharmacodynamic (where pharmacokinetic properties are unchanged, but the effects of a drug are either exaggerated or diminished). Although many combinations of medications can be safely used together, at least 1 analysis of a claims database has estimated the risk of exposure to a clinically meaningful drug interaction to be in excess of 6%/year (2). Given the high incidence of cardiovascular disease and the use of multiple drugs during and after PCI, DDI that might affect procedural or late outcomes are very important. This review examines potential DDI in the periprocedural term of PCI.

Drug–drug interactions can be difficult to identify. Although altered concentrations of drugs can be objectively measured for most medications in research settings, it is more difficult to describe the clinical impact. Often, there are very few data about the clinical effects of sub- or supra-therapeutic concentrations of drugs in humans. Additionally, commercial bioassays are only available for selected medications, making many DDI "theoretical" or reliant on presentation of clinical sequelae before suspicion is raised. In contrast, some DDI produce measurable pharmacokinetic or pharmacodynamic changes, but these have little effect on clinical outcomes. Large-scale, prospective clinical assessments examining the impact of DDI are rare. Although drugs in development are tested in combination with commonly prescribed medications for the particular disease state, such assessments are limited. Rather, many DDI are retrospectively identified and described via case reports or case series. These issues lead to difficulty in determining causality or whether a DDI is clinically meaningful in practice. To aid in this process, several scoring systems have been developed. Austin Bradford-Hill criteria, developed to determine association with causality, have been applied to studies of potential DDI (3). Recently, the Drug Interaction Probability Scale (Table 1) has been developed to more specifically address causality of a DDI with a clinical adverse event (4).

Although the possibility of multiple DDI exists with the medication regimen of any patient when presenting for a cardiac intervention, this review will focus on DDI that have the potential to affect procedural outcomes, either through increases in procedural complications or compromising

longer-term procedural success. A brief discussion of other DDI that are highly likely in a patient with coronary artery disease is also provided.

Anticoagulants

Anticoagulants (e.g., heparins and direct thrombin inhibitors) in combination with antiplatelet therapies remain the standard of care to minimize thrombotic complications in acute coronary syndromes and PCI. Most DDI with anticoagulant therapies are pharmacodynamic. There are multiple anticoagulants available with many targets in the coagulation cascade, potentially exposing the patient to increased bleeding complications (Table 2). Likewise, several oral anticoagulants are now available that can affect periprocedural events as well as long-term outcome.

Oral Anticoagulants at the Time of PCI

Oral anticoagulation with vitamin K antagonists (e.g., warfarin) is often administered to patients with cardiovascular disease. Although the exact frequency is uncertain, it is estimated that approximately 5% percent of all patients undergoing PCI are receiving chronic anticoagulation therapy (5). Warfarin depletes vitamin K-dependent clotting factors II, VII, IX, and X, which is a broader impact than most anticoagulants used during PCI (Factors Xa and IIa). This combination of broad-target factor-depleting drugs and potent inhibitors of activated factors can markedly increase the bleeding risk.

The outcomes among warfarin-treated patients undergoing PCI have been evaluated in both single and multicenter registries and trials with variable results. The National Cardiovascular Data Registry database revealed that 3.6% of patients undergoing PCI were receiving warfarin at the time of the procedure (6). Increases in in-hospital bleeding (elective PCI: 3.2% vs. 1.9%, adjusted odds ratio [OR]: 1.26, 95% CI 1.09 to 1.46; urgent PCI: 8.2% vs. 4.8%, adjusted OR: 1.42, 95% CI 1.14 to 1.76) were observed, compared with patients not receiving warfarin. Differences in unadjusted in-hospital mortality (elective PCI: 1.4% vs. 0.6%, $p < 0.001$; urgent PCI: 8.6% vs. 4.5%, $p < 0.001$) were also observed. Similarly, an analysis of the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) registry, a voluntary, observational registry designed to improve the care of patients with unstable angina and non–ST-segment elevation myocardial infarction, revealed that those patients receiving warfarin were less likely to undergo PCI (36.8% vs. 51.8%, adjusted OR: 0.80, 95% CI 0.75 to 0.86) and also less likely to receive important antiplatelet therapies, such as aspirin (90.6% vs. 95.9%, adjusted OR: 0.52, 95% CI 0.46 to 0.57) and clopidogrel (37.7% vs. 55.6%, adjusted OR: 0.53, 95% CI 0.50 to 0.56) (7). These patients also had delayed time to PCI. Warfarin-treated patients had increased rates of blood transfusions (13.2% vs. 9.0%, adjusted OR: 1.09, 95% CI 1.00 to 1.19) and substantially increased rates of major bleeding (13.8% vs. 9.0%, adjusted OR: 1.88, 95% CI 1.48 to 2.38) when receiving co-administration of glycoprotein IIb/IIIa inhibitors.

Because of bleeding concerns, caution is needed for patients being treated with warfarin who present for PCI, although there are limited evidence-based data. Guidance suggests the International Normalized Ratio (INR) should be ≤1.8 for femoral cases and that patients with therapeutic INRs should generally have elective PCI procedures delayed until the INR falls to within this level (8). However, given the urgent/emergent nature of many coronary interventions, this might not be acceptable. Although reversal of INR is possible, it might take 12 to 24 h after the administration of phytonadione (vitamin K), and full reversal is generally not advisable, because resistance to anticoagulation has been demonstrated upon re-initiation of warfarin in vitamin K-treated patients. Administration of periprocedural fresh frozen plasma or other factor products is also an option, but this might be impractical in an emergency intervention and is only effective for a limited time frame. Regardless, patients receiving oral anticoagulants should be identified before the procedure, if possible, and a strategy should be developed to minimize both bleeding risks from the procedure and thrombotic risk from lack of this drug therapy. An important strategy is the use of the radial artery to decrease bleeding risk, although the INR is not recommended to exceed 2.2 for these cases (8).

Abbreviations and Acronyms

ACS = acute coronary syndromes
AUC = area under the curve
CCB = calcium channel blocker
COX = cyclooxygenase
DDI = drug–drug interactions
DHP = dihydropyridine
FDA = U.S. Food and Drug Administration
GI = gastrointestinal
INR = International Normalized Ratio
NSAID = nonsteroidal anti-inflammatory drug
PCI = percutaneous coronary intervention
PPI = proton pump inhibitor
UFH = unfractionated heparin

Recently, new oral anticoagulants have been approved for use in humans that specifically target either Factor IIa (dabigatran) or Factor Xa (apixaban, rivaroxaban). To date, no definitive evaluation of the efficacy or safety of these drugs in the setting of PCI has been performed. However, the use of rivaroxaban in acute coronary syndromes (ACS) patients has been evaluated in the ATLAS-2 (Anti Xa Therapy to Lower cardiovascular events in addition to standard therapy in subjects with Acute Coronary Syndrome) trial, whereupon 2.5- and 5-mg twice daily dosing regimens (9) in addition to standard therapy after revascu-

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 12, 2012
DECEMBER 2012:1195–208

Table 1. Elements of the Drug Interaction Probability Scale

Factor	Score* Assigned If Yes	Score* Assigned If No†
Previous credible reports of the interaction in humans	+1	−1
Observed interaction consistent with interactive properties of precipitant drug	+1	−1
Observed interaction consistent with interactive properties of object drug	+1	−1
Event consistent with the known or reasonable time course of the interaction (onset and/or offset)	+1	−1
Interaction remitted upon dechallenge of the precipitant drug with no change in the object drug	+1	−2
Interaction reappeared when the precipitant drug was re-administered in the presence of continued use of object drug	+2	−1
Reasonable alternative causes for the event	−1	+1
Object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction	+1	0
Drug interaction confirmed by objective evidence consistent with the effects on the object drug	+1	0
Interaction greater when the precipitant drug was increased or less when precipitant drug decreased	+1	−1

See Horn et al. (4). *Total score >8 = highly probable; 5 to 8 = probable; 2 to 4 = possible; and <2 = doubtful. †If unknown or not applicable, 0 points are assigned.

larization procedures reduced the risk of ischemic events and increased the risk of bleeding events. Several other studies of Factor Xa inhibitors have been discontinued due to excessive bleeding. Therefore, at present, elective PCI should not be performed during exposure to these newer agents and should be delayed in a time frame consistent with the pharmacological offset of each agent (Table 2). Optimal reversal strategies for urgent or emergent procedures in patients receiving these medications have not been determined.

Parenteral Anticoagulants at the Time of PCI

During the treatment of ACS, patients might be transitioned from one anticoagulant strategy to another. This can be problematic, leading to unpredictable "stacking" of anticoagulant effects due to differences in pharmacokinetics and drug clearance among anticoagulants. The reasons that "anticoagulant mixing" or "anticoagulant crossover" occurs are multiple and understandable, because numerous effective agents and combinations are available. There are valuable data on the frequency and clinical impact of anticoagulation mixing in patients with ACS and PCI. The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors) trial, which compared enoxaparin and unfractionated heparin (UFH) in the medical treatment of ACS undergoing an early interventional approach (10), demonstrated increased rates of bleeding with crossover, regardless of whether

Table 2. Characteristics of Anticoagulants Used in Patients Undergoing Cardiac Catheterization

Medication	Mechanism of Action	Approximate Pharmacological Onset	Approximate Pharmacological Offset	Clinical Considerations
Apixaban	Direct factor Xa inhibitor	Oral: 3–4 h	24 h	Hepatic and/or renal dysfunction will prolong elimination
Argatroban	Direct thrombin inhibitor	Bolus: immediate Infusion (no bolus): 2–3 h	2–4 h	Hepatic dysfunction will prolong elimination
Bivalirudin	Direct thrombin inhibitor	Bolus: immediate Infusion (no bolus): 2 h	2 h	Renal dysfunction will prolong elimination
Dabigatran	Direct thrombin inhibitor	Oral: 1–2 h	24–48 h	Renal dysfunction will prolong elimination
Enoxaparin	Low-molecular weight heparin; cofactor for antithrombin inhibition of primarily factor Xa	Intravenous: immediate Subcutaneous: 4–6 h	12 h	Renal dysfunction will prolong elimination
Fondaparinux	Co-factor for antithrombin inhibition of factor Xa	Intravenous: immediate Subcutaneous: 2–3 h	24 h	Renal dysfunction will prolong elimination Doses recommended for acute coronary syndromes do NOT result in therapeutic anticoagulation, and combination therapy with heparin is recommended for interventional procedures
Heparin (unfractionated)	Co-factor for antithrombin inhibition of factor IIa and Xa	Bolus: immediate Infusion (no bolus): 6 h	4–6 h	
Rivaroxaban	Direct factor Xa inhibitor	Oral: 2–4 h	24 h	Hepatic and/or renal dysfunction will prolong elimination

patients crossed from UFH to enoxaparin or vice versa (11). Mixing strategies with enoxaparin were prospectively tested in the STACKENOX (STACK-on to ENOXaparin) study, where 72 healthy subjects who were receiving enoxaparin were randomized to UFH 4, 6, or 10 h after the last dose of enoxaparin (12). Anti-Xa activity was increased at all time-points, suggesting longer duration of discontinuation is warranted when attempting to switch patients from enoxaparin to UFH. Other anticoagulant strategies suggest crossovers have less relevant impact on clinical outcomes. The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial of ACS patients undergoing PCI demonstrated no change in ischemic endpoints when patients were crossed over from UFH or enoxaparin to bivalirudin (13). In contrast, there was approximately a 50% reduction in major bleeding events among patients switched to bivalirudin. Furthermore, patients in the OASIS-5 (The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial receiving fondaparinux were recommended to receive UFH at the time of PCI due to an early excess in procedural thrombotic complications (14). This approach has also been suggested by guidelines (15). Table 2 illustrates various anticoagulants that might be used in the periprocedural setting, their mechanism of action, and onset/offset of action.

Guidelines have generally recommended maintaining anticoagulant consistency throughout the ACS- to -PCI spectrum (15), due mainly to the adverse clinical effects of anticoagulant crossover demonstrated in the SYNERGY trial. As mentioned in the preceding text, a notable exception to this is the therapeutic benefit of adding UFH to patients undergoing PCI being treated with fondaparinux. Although some data suggest that switching anticoagulants can be done safely, this should occur in a systematic way (Table 2).

Antiplatelets and Oral Anticoagulants After PCI

Patients undergoing PCI often have indications for long-term oral anticoagulant therapy with warfarin derivatives. The combination of warfarin with oral antiplatelet therapy after PCI has been associated with increased rates of bleeding, despite the medical necessity of both therapies. Andreotti et al. (16), in a meta-analysis of 10 studies with 7,836 patients receiving aspirin plus warfarin versus those receiving warfarin alone after ACS, demonstrated that combination therapy (warfarin plus aspirin) was associated with increased rates of major bleeding events compared with aspirin only (OR: 2.32, 95% CI 1.63 to 3.29). The problem is compounded further because most post-PCI patients receive aspirin and thienopyridines after stent implantation. The risk of triple therapy was evaluated by Mattichak et al. (17), where 40 patients receiving triple therapy were compared with 42 patients receiving standard dual antiplatelet therapy (aspirin plus clopidogrel) after PCI. A trend in increased bleeding (15% vs. 9%) and an increase in the number of transfusions were seen in patients receiving triple therapy. Khurram et al. (18) and Rogacka et al. (19) also observed an increase in bleeding events after PCI in patients receiving triple therapy versus dual antiplatelet therapy. Conversely, an analysis of the GRACE registry (Global Registry of Acute Coronary Events) of 580 patients receiving triple therapy revealed no overall increase in the risk of major bleeding events between warfarin plus dual antiplatelet therapy versus warfarin plus single antiplatelet therapy (5.9% vs. 4.6%, $p = 0.46$) (20). In fact, reductions in the incidence of ischemic stroke were observed with triple therapy versus dual antiplatelet therapy (0.7% vs. 3.4%, respectively, $p = 0.02$).

Overall, observational evidence with regard to the risk of bleeding events prompted more formal guidance from the American College of Cardiology in 2009, when several strategies were promoted that were designed to minimize the bleeding risk when dual antiplatelet therapy and warfarin must be used together (21). These include minimizing the aspirin dose to 75 to 81 mg daily, lowering the INR goal to 2.0 to 2.5 (depending on the indication for anticoagulation), and prophylactic use of gastroprotective strategies, including proton pump inhibitors (PPIs). However, clinicians should be cautious and avoid exposure to "triple therapy" if possible, including re-evaluation of the indications for both antiplatelet therapy and warfarin. In addition, it might be prudent to avoid scenarios in which long-term dual antiplatelet therapy is routinely administered in patients with chronic indications for anticoagulation (e.g., drug-eluting stent placement). The use of PPIs in patients receiving clopidogrel is controversial, as discussed in the following text. No formal evaluation of more potent $P2Y_{12}$ inhibitors (e.g., prasugrel, ticagrelor) in combination with oral anticoagulants has occurred, adding more uncertainty to the risk of bleeding when these agents are employed.

Antiplatelets

Aspirin. Aspirin, along with $P2Y_{12}$-inhibitor therapy, is essential in the maintenance of stent patency and in the primary and secondary prevention of myocardial infarction. Drug–drug interactions with aspirin primarily exist in the form of pharmacodynamic interactions based on overlapping anti-hemostatic mechanisms. However, some interactions where aspirin effectiveness can be altered have been promoted, primarily through the competitive inhibition of the acetylation site of cyclooxygenase (COX) in the platelet.

Although aspirin does have nonsteroidal anti-inflammatory (NSAID) properties, its use as an analgesic is limited due to excessive adverse gastrointestinal (GI) events at higher doses. Therefore, traditional NSAIDs, such as ibuprofen and naproxen, and COX-2 selective agents, such as cele-

coxib, are likely to be used in addition to aspirin in patients who require chronic analgesic control, particularly those with osteoarthritis. Additionally, NSAID therapy might be used in the setting of pericarditis to reduce inflammation, which might occur in post-interventional patients after acute myocardial infarction. Because the antiplatelet effect of aspirin is dependent on adequate inhibition of COX-1, it is theoretically possible that competitive inhibition of COX-1 by other NSAIDs might lessen the antiplatelet efficacy of aspirin, particularly non–COX-2 selective agents. A randomized, prospective, open-label, crossover study demonstrated that the antiplatelet effect of aspirin was significantly diminished when 400 mg of ibuprofen was administered 2 h before 81 mg of aspirin (22). In this study, patients received 6 consecutive days of aspirin (81 mg) administered 2 h before ibuprofen (400 mg) followed by a 2-week washout, followed by the same regimen but with the reversed administration (ibuprofen 2 h before aspirin administration). Serum thromboxane B_2 levels measured 24 h after study drug administration on Day 6 were maximally reduced in the patients receiving aspirin before ibuprofen (mean percentage inhibition: 99 ± 0.3 [SD]) but were only moderately reduced when ibuprofen was taken before aspirin (mean percentage inhibition: 53 ± 7 [SD]) ($p < 0.001$). Another prospective trial evaluating the antiplatelet effect of aspirin in both ibuprofen- and celecoxib-treated patients identified that ibuprofen-treated patients had significantly higher levels of platelet aggregation compared with patients not receiving ibuprofen (23). Additionally, a retrospective cohort evaluation of 7,107 aspirin-treated patients identified that patients taking ibuprofen had a higher risk of all-cause mortality compared with nonusers (hazard ratio: 1.93, 95% CI 1.30 to 2.87, $p = 0.0011$) (24). On the basis of these data, the American Heart Association issued a Scientific Advisory in which they suggest that this interaction might be clinically significant (25). The U.S. Food and Drug Administration (FDA) further recommended separating the timing of administration of aspirin such that it is taken 30 min before the receipt of ibuprofen or 8 h after the dose (26). The effects of NSAIDs on COX are reversible, such that the molecule releases from the binding site after the 8-h time frame post-administration. However, this dosing suggestion would only apply to non–enteric-coated aspirin products. No specific recommendation regarding timing of enteric-coated aspirin products—which purposefully delay absorption—is provided. Catella-Lawson et al. (22) demonstrated that the antiplatelet effect of aspirin is attenuated if ibuprofen is administered up to 12 h after enteric-coated aspirin administration. Data are less clear with other NSAIDs but are suggestive in total that nonselective NSAIDs (e.g., indomethacin, naproxen) also interfere with the antiplatelet effects of aspirin in a similar manner as ibuprofen, whereas use of more COX-2 selective agents (e.g., celecoxib, diclofenac, meloxicam) likely do not interfere with aspirin (27–29).

Thienopyridine $P2Y_{12}$ inhibitors. Thienopyridines, including ticlopidine, clopidogrel, or prasugrel, are uniformly used for a variable duration in all patients undergoing stent implantation and in an increasing number of patients treated medically for ACS. Therefore, DDI affecting the efficacy or safety of thienopyridines have tremendous implications.

Many theoretical DDI with thienopyridines involve pharmacokinetic interactions that interfere with the metabolic conversion of the parent compound to the active metabolite. Thienopyridines are prodrugs, requiring conversion by the liver via the CYP450 system before the desired clinical effect is achieved. Clopidogrel requires a 2-step conversion with an intermediate metabolite via some combination of CYP3A4, 1A2, 2C9, 2C19, and 2B6 (30). Prasugrel has a more simplified metabolism, requiring only a 1-step conversion via CYP3A4 and 2B6 (31). The precise contribution of each isoenzyme and what, if any, compensatory changes might take place have been difficult to assess in vivo, given that the active metabolite is unstable and difficult to measure. Drugs that interfere with or are co-metabolized through that particular metabolic pathway might decrease the antiplatelet effect of thienopyridines and expose the patient to increased risk of thrombotic events.

PPIs. Proton pump inhibitors—including omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole—are widely used in the treatment and prevention of acid-related GI disorders. They are among the most widely used drugs in the world and are also recommended as first-line protective therapy against drug-induced gastric erosion and bleeding events with dual antiplatelet therapy (32). However, PPIs also have varying affinity and inhibitory properties of the isoenzyme CYP2C19, which might theoretically reduce biotransformation to the active metabolite and increase the risk of clinical events. Interference with the antiplatelet effects of clopidogrel by the concomitant use of PPIs has been suggested in multiple clinical trials (33–36). Data regarding the clinical significance of a thienopyridine–PPI interaction seem to be mixed. Many (37–39) but not all (40,41) observational studies of registries or claims data seem to indicate risk with co-administration, but such data might be at risk of confounding bias or more subject to methodological error. Analyses of randomized controlled clinical trials have been more uniform in demonstrating no significant clinical impact of PPI use on the clinical benefit seen with thienopyridines. An analysis of the TRITON (Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel) study demonstrated that PPI use had no clinical impact on the efficacy or safety of prasugrel or clopidogrel (35). Additionally, a prospective randomized controlled trial of a novel dosage formulation (CGT-2168) evaluated clopidogrel and omeprazole versus placebo in the COGENT-1 (Clopidogrel and the Optimization of Gas-

trointestinal Events) trial in 3,627 patients after ACS (42). Although the study was primarily designed to examine GI safety endpoints, cardiovascular events were also identified, although the study was not adequately powered to measure these events. The study was terminated prematurely due to lack of funding, and the mean follow-up period was only 133 days. Overall, the study showed no significant difference between omeprazole and placebo in ischemic outcomes, and GI safety outcomes favored the combination product of clopidogrel and omeprazole. Although the COGENT-1 trial represents the strongest data to date that the interaction between clopidogrel and PPIs is not clinically significant, limitations such as potential differences in release kinetics, a relatively short follow-up, and that the trial was not primarily designed to address cardiovascular safety make this a continued source of controversy. Recently, the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association released a consensus statement summarizing evidence regarding the clopidogrel–PPI interaction and recommended that a careful assessment of the risk-benefit profile of the patient with regard to GI bleeding and cardiovascular event risk take place. In addition, PPIs might still be recommended in high-risk patients receiving dual antiplatelet therapy (43). The FDA has also recommended avoiding the concomitant use of clopidogrel and omeprazole or esomeprazole, despite the lack of any significant guidance from major cardiovascular organizations (44). Although controversy remains with regard to this decision, it seems prudent to avoid these specific combinations at the present time. The use of pantoprazole or rabeprazole might be considered preferential for high-risk GI patients requiring the use of clopidogrel due to their lesser affinity for CYP2C19. The use of certain histamine antagonists (famotidine, ranitidine) should also be considered as first-line therapy in preference to PPIs, which are not metabolized through the CYP450 system. The use of prasugrel or ticagrelor instead of clopidogrel might also be considered if a CYP2C19-inhibiting PPI must be used, although this must be weighed against a likely increase in bleeding risk.

STATINS. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ("statins") are indicated in virtually every patient undergoing vascular intervention and would be highly likely to be co-administered with clopidogrel. Mechanistically, statins were hypothesized to blunt the effect of clopidogrel due to varying degrees of competitive metabolism through CYP3A4 (45), a known pathway in the conversion of the clopidogrel parent compound to its active metabolite. This hypothesis was first examined by Lau et al. (46) in a randomized, controlled trial examining the effects of increasing atorvastatin doses in clopidogrel-treated patients on ex-vivo platelet function. The study found that increased atorvastatin doses decreased platelet function in clopidogrel-treated patients in a linear manner, with doses of 40 mg and larger completely attenuating the effects of clopidogrel. However, multiple subsequent pharmacodynamic studies of the effect of both atorvastatin (47,48) as well as other statin drugs (49–51) have identified no effect of co-administration on ex-vivo mediated platelet function. Analyses of the CREDO (Clopidogrel for the Reduction of Events During Observation) (52), CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) (53), and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trials (54) have demonstrated no impact of statin use on clinical events in clopidogrel-treated patients. On the basis of these data, there is no suggestion or recommendation to modify statin therapy in patients receiving clopidogrel or other thienopyridines.

CALCIUM CHANNEL BLOCKERS. Calcium channel blockers (CCBs) are often co-administered in patients being treated with thienopyridines. It has been speculated that certain CCBs, which inhibit CYP3A4 (verapamil, diltiazem), might interfere with the biological conversion of clopidogrel to its active metabolite. This concept has been examined by 2 studies of exvivo mediated platelet function in clopidogrel-treated patients. Siller-Matula et al. (55) demonstrated that clopidogrel-treated patients receiving CCB therapy had higher platelet-reactivity index values than patients not receiving CCB. These findings were supported by Gremmel et al. (56) in which clopidogrel-treated patients receiving CCBs had higher levels of ADP-induced platelet aggregation compared with patients not receiving a CCB. To date, only 1 evaluation of the clinical impact of CCB therapy on the efficacy of clopidogrel has been performed, using patients enrolled in the CREDO trial. Overall, there was no significant difference in the 1-year primary composite endpoint of death, myocardial infarction, or stroke in CCB-treated patients compared with non–CCB-treated patients (57). On the basis of these findings, there is no recommendation for modification of clopidogrel therapy in patients receiving a CCB at this time, although more clinical data are needed for this to be definitive.

AZOLES. Azole antifungal drugs, including ketoconazole, itraconazole, fluconazole, voriconazole, and posaconazole, are used in many patients not only to treat fungal infections but also to prevent fungal infections in high-risk patients. By nature, these drugs will most likely be co-administered to patients in short-term courses, with the most common exception being the need for long-term co-administration for fungal prophylaxis in a patient who has received an organ transplant, including heart transplantation. The azole antifungals inhibit the isoenzyme CYP3A4 (58), although this can vary within the class, with ketoconazole perhaps being the strongest inhibitor and fluconazole the most moderate (59). Ketoconazole in particular is such a strong inhibitor that it is often used in clinical trials to determine

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 12, 2012
DECEMBER 2012:1195–208

the potential for a pharmacokinetic-related DDI with CYP3A4-metabolized medications. Because clopidogrel is partially converted through the CYP3A4 system to its active metabolite, it has been felt that the azole antifungals might interfere with this process. In 1 study, ketoconazole co-administration to clopidogrel-treated patients did indeed decrease the active metabolite formation of clopidogrel and attenuate the pharmacodynamic effect on platelet function but did not affect prasugrel-treated patients (60). However, there have been no clinical descriptions of clinical worsening of clopidogrel-treated patients with azole antifungals. In addition, the impact of more commonly used azoles, such as voriconazole and fluconazole, are unknown. At this time, there is no recommendation for therapeutic modification of azole antifungals in thienopyridine-treated patients.

WARFARIN. Warfarin affects a variety of vitamin K-dependent clotting factors and is also well known for its potential for DDI. Warfarin is metabolized by multiple cytochrome P450 enzymes, including both CYP2C9 and CYP3A4, both of which also are important in the conversion of clopidogrel to its active metabolite. The potential for warfarin to interfere with the antiplatelet efficacy of clopidogrel was first identified by Sibbing et al. (61), in which patients receiving clopidogrel and phenprocoumon were found to have greater platelet aggregation compared with patients receiving clopidogrel only. Several observational studies of clopidogrel and warfarin derivatives have been performed as well. Most of these studies have examined the bleeding risk associated with this combination and not whether the combination is associated with increased platelet-mediated thrombosis. However, at least 1 large retrospective analysis of the GRACE registry did not demonstrate increase bleeding with the combination (20), which might theoretically be explained by warfarin decreasing the antiplatelet efficacy of clopidogrel. Observational studies of the ischemic risk of the combination might also be difficult, due to increased bleeding events resulting in a high percentage of "supply-demand" types of myocardial infarctions, which might be difficult to control for in an observational study. To date, there is no recommendation for therapeutic modulation on the basis of affecting the efficacy of clopidogrel, although, as mentioned, several recommendations have been made with regard to avoidance of the bleeding effects of the combination of clopidogrel, aspirin, and warfarin (21).

Non-thienopyridine $P2Y_{12}$ inhibitors. Ticagrelor is a novel, non-thienopyridine $P2Y_{12}$ antagonist recently approved for use in the setting of ACS-related PCI. Unlike thienopyridines, ticagrelor is not a prodrug and does not require hepatic metabolism before becoming biologically active. Ticagrelor is eliminated through the liver, primarily via the CYP3A4 system. As such, strong CYP3A4 inhibitors (e.g., ketoconazole, voriconazole, clarithromycin, protease inhibitors) are contraindicated with ticagrelor, because they might significantly increase exposure to the drug and expose the patient to toxic effects, such as bleeding (62). Similarly, strong CYP3A4 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine) are also contraindicated with ticagrelor and might result in thrombotic events, such as stent thrombosis.

Interestingly, aspirin dose seems to be negatively associated with ticagrelor benefit. In a post hoc analysis of the PLATO (PLATelet inhibition and patient Outcomes) trial, the North American cohort failed to show benefit of ticagrelor over clopidogrel (63). This result has been attributed to the practice of using higher maintenance doses of aspirin in the United States. In a multivariate analysis of the entire PLATO study, aspirin doses $\geq$300 mg/day predicted adverse outcomes in the trial population (hazard ratio: 1.45, 95% CI 1.01 to 2.09). Currently, there is no definitive biological rationale that explains these findings, but it is speculated that reductions in platelet-inhibiting prostacyclins produced by higher doses of aspirin might blunt the clinical benefits associated with ticagrelor. Although it is also entirely possible this interaction represents a chance finding (64), the FDA has added a boxed warning to the ticagrelor labeling, recommending limiting the dose of aspirin to $\leq$100 mg/day when used with ticagrelor (62).

Sedatives/analgesics. Conscious sedation modalities are employed in most interventional settings (8,65). Typically, this consists of a short-acting intravenous or oral benzodiazepine and a short-acting intravenous opiate. Although this combination is therapeutically advantageous, it might also represent a potentially adverse pharmacodynamic DDI due to the synergistic effects on respiratory depression and should be applied in a systematic way with appropriate monitoring of both the level of sedation as well as key safety indicators, such as cardiac and respiratory function (66). In addition, benzodiazepines and opiates are extensively metabolized by the liver and are therefore subject to potential DDI from agents that might affect liver metabolism.

Benzodiazepines. Benzodiazepines used in interventional procedures include midazolam, lorazepam, and diazepam. In general, many of the benzodiazepines are hepatically metabolized by the CYP450 system to active or inactive metabolites, especially via CYP3A4 (67). Therefore, classically "strong" CYP3A4 inhibitors might result in prolonged or excessive sedation in these patients when used concurrently. In addition, several cardiac medications that are competitively metabolized through CYP3A4 have been specifically studied with procedural benzodiazepines. McDonnell et al. (68) demonstrated that co-administration of atorvastatin in patients receiving intravenous midazolam undergoing general anesthesia resulted in an increase in the area-under-the-curve (AUC) and a decrease in the clearance of midazolam. Although atorvastatin in particular was examined in this trial, most CYP3A4-metabolized statins

likely carry similar risk, including simvastatin and lovastatin. In addition, studies of diltiazem and verapamil have also demonstrated increases in the peak concentration, AUC, and a decrease in the clearance of intravenous midazolam (69). A combination of non-dihydropyridine (DHP) CCBs and midazolam has also been shown to result in more profound and prolonged sedation than non-exposure to the interaction (70). Although none of these interactions would necessarily result in toxic exposure to sedating medications in the setting of appropriate monitoring, the presence of a CYP3A4 inhibitor or CYP3A4-metabolized drug might result in deeper and longer-than-expected sedation periods, which might potentially expose the patient to risk of severe respiratory depression. Careful attention to level of sedation is required when using benzodiazepines in patients receiving CYP3A4 inhibitors or co-metabolized drugs, and cardiac catheterization conscious sedation protocols should be conservative and provide more frequent monitoring in comparison with other procedural areas. Another alternative would be to use a nonoxidatively metabolized benzodiazepine (e.g., lorazepam) (67), but the longer duration of action might offset any potential gain reached with avoidance of the DDI.

Opiates. Opiate medications used to relieve pain and facilitate sedation during PCI include fentanyl, morphine, and hydromorphone, among others. The vast majority of opiate medications are hepatically metabolized through the CYP450 system, and most are hepatically metabolized via the CYP3A4 isoenzyme (71). Therefore, strong CYP3A4 inhibitors or co-metabolized drugs might increase the level of sedation and prolong its effects in patients exposed to the DDI, similarly to benzodiazepines. Commonly used cardiac medications that inhibit CYP3A4 or are metabolized through CYP3A4 include non-DHP CCBs and statin medications. In particular, non-DHP CCBs have multiple reports of pharmacokinetic interactions or clinically significant DDI when administered with fentanyl (70,72). A careful approach is warranted, like with benzodiazepines, when using CYP3A4-altering or metabolized medications in patients receiving opiates for interventional procedures. Conscious sedation protocols for the catheterization laboratory should be conservative and include more frequent monitoring compared with other procedural areas, given the pervasive use of statins in the periprocedural setting.

Statins

The potential interaction of statins with clopidogrel therapy and procedural sedation was discussed previously. However, statins themselves might be subject to a significant number of pharmacokinetic DDI, particularly statins that are primarily metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin). Inhibition of statin metabolism is likely to produce an increase in the frequency of muscle-related toxicities, including rhabdomyolysis. Several of these interactions are known to exist in cardiovascular medicine.

Fibrates. Statins and fibric acid derivatives such as gemfibrozil, fenofibrate, and fenofibric acid are a potentially attractive combination of medications to treat mixed dyslipidemias and have been used together in practice for some time. However, increased adverse events have been reported with this combination. Gemfibrozil specifically seems to alter statin bioavailability through a multitude of mechanisms—unlike DDI with most statin medications—including inhibition of statin uptake in the liver through ATP-cassette binding proteins and organic anion transporters (73). Inhibition of CYP450 enzymes might also play some role. This interaction results in an increase in statin concentration independent of the iosenzyme pathway through which it is metabolized.

Several pharmacokinetic studies of gemfibrozil and various statins have been performed. Overall, co-administration of gemfibrozil and statins has resulted in a 185% increase in the AUC of simvastatin (74), a 35% increase in the AUC of atorvastatin (75), and an 88% increase in the AUC of rosuvastatin (76). Clinical data also exist that describe the adverse impact of this DDI. Several case reports have described severe adverse effects, such as rhabdomyolysis with both simvastatin and atorvastatin (77–79). An analysis of the FDA reporting system revealed 384 reports of rhabdomyolysis with a statin-fibrate combination, with most of these (88%) requiring hospital stay for renal failure (80). Another study evaluating rhabdomyolysis rates in patients receiving both statins and fibrates found that gemfibrozil use increased the rate of rhabdomyolysis associated with statins by 1 to 2 orders of magnitude compared with monotherapy (81).

Regulatory bodies and professional societies have expressed caution with the concomitant prescription of a statin and a fibrate due to these findings. When using gemfibrozil with a statin, a maximum dose of 10 mg/day of rosuvastatin and a maximum of 20 mg/day with lovastatin is recommended (82,83). Furthermore, the use of simvastatin and gemfibrozil is now contraindicated after the recent completion of safety review by the FDA (84). Specific dosing recommendations are not provided for atorvastatin or pravastatin, but dose reduction is likely warranted on the basis of the increases in AUC that have been identified by pharmacokinetic studies. Lesser alteration of statin concentrations has also been shown when paired with fenofibrate or fenofibric acid, and clinical reports of rhabdomolysis are significantly lower than those identified with gemfibrozil (75), suggesting that fenofibrate be preferentially considered when combination therapy for mixed dyslipidemia is warranted. The use of fluvastatin as the statin of choice might also be considered, but the reduced potency of that agent

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 12, 2012
DECEMBER 2012:1195–208

Table 3. Drug–Drug Interactions and Recommended Management in Interventional Cardiology

Drug Interaction	Mechanism	Recommendation
Oral anticoagulants and procedural anticoagulants	Pharmacodynamic; potential to inhibit multiple clotting factors and maintain a minimal level of hemostasis; increases bleeding risk	For elective procedures, hold oral anticoagulant in a time frame consistent with pharmacological offset For urgent or emergent procedures, consider use of hemostatic agents (fresh frozen plasma, factor products) if necessary; consider radial access as preferential for cath
Parenteral anticoagulants and procedural anticoagulants	Pharmacodynamic; potential to inhibit multiple clotting factors and maintain a minimal level of hemostasis; increases bleeding risk	Maintain consistent use of anticoagulant throughout ACS to PCI spectrum. Develop an institution-specific protocol that allows for anticoagulant switching to occur in time frames based on pharmacological and clinical evidence
Dual antiplatelet therapy and oral anticoagulants	Pharmacodynamic; inhibition of platelet and clotting factor driven thrombosis; increases risk of bleeding	Evaluate indication for chronic use of both dual antiplatelet therapy and oral anticoagulant For warfarin—target INR of 2.0–3.0, use low-dose aspirin (75–81 mg daily) and consider gastric protection with PPI No data regarding the risk of bleeding with more potent $P2Y_{12}$ inhibitors (prasugrel, ticagrelor) or with newer oral anticoagulants (apixaban, dabigatran, Rivaroxaban)
Aspirin and NSAIDs	Competitive inhibition of COX-1 might lessen aspirin's COX-1 mediated inhibition of thromboxane A2 and increase the risk of thrombotic events	Regular-release aspirin should be administered before (30 min) or 8 h after nonselective NSAID therapy (e.g., ibuprofen, indomethacin, naproxen) in patients receiving continuous NSAID therapy. Patients receiving COX-2 selective agents (e.g., celecoxib, meloxicam, sulindac) likely do not require altered administration. Consider avoiding the use of enteric-coated aspirin products in patients receiving nonselective NSAIDs.
Clopidogrel and PPIs	Prevents metabolic conversion of clopidogrel to active metabolite via inhibition of CYP2C19; might increase risk of thrombotic events, including stent thrombosis	Avoid concomitant use of clopidogrel with either omeprazole or esomeprazole Evaluate indication for PPI therapy. If indicated, preferentially use pantoprazole or rabeprazole. Consider histamine-blocker therapy as first-line for reflux disease.
Clopidogrel and statins	Prevents metabolic conversion of clopidogrel to active metabolite via competitive metabolism through CYP3A4; might increase risk of thrombotic events, including stent thrombosis	No recommendation to avoid use or modify therapy if co-administered
Clopidogrel and calcium channel blockers	Prevents metabolic conversion of clopidogrel to active metabolite via competitive metabolism through or inhibition of CYP3A4; might increase risk of thrombotic events, including stent thrombosis	No recommendation to avoid use or modify therapy if co-administered
Clopidogrel and azole antifungals	Prevents metabolic conversion of clopidogrel to active metabolite via inhibition of CYP3A4; might increase risk of thrombotic events, including stent thrombosis	No recommendation to avoid use or modify therapy if co-administered
Clopidogrel and warfarin	Pharmacodynamic—potential for increased risk of bleeding Might prevent conversion of clopidogrel to active metabolite via competitive metabolism through CYP2C9 and CYP3A4 and increase risk of thrombotic events, including stent thrombosis	See "Dual Antiplatelet Therapy and Oral Anticoagulants" section for recommendations regarding reducing the risk of bleeding if co-administration necessary. No specific recommendation regarding potential for decreased clopidogrel effectiveness at this time.
Ticagrelor and CYP3A4 inhibitors	Prevents metabolism of ticagrelor via CYP3A4 and might increase the risk of bleeding	Administration of ticagrelor and strong CYP3A4 inhibitors (e.g., ketoconazole, voriconazole, clarithromycin, protease inhibitors) is contraindicated
Ticagrelor and CYP3A4 inducers	Increases metabolism of ticagrelor via CYP3A4 and might increase the risk of thrombotic events, including stent thrombosis	Administration of ticagrelor and strong CYP3A4 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine) is contraindicated
Ticagrelor and aspirin	Unknown; higher aspirin doses might interfere with the antiplatelet effects of aspirin and increase the risk of thrombotic events	Aspirin dose should not exceed 100 mg/day when used with ticagrelor

Continued on next page

Table 3. Continued

Drug Interaction	Mechanism	Recommendation
Benzodiazepines and statins	Prevents metabolism of oxidatively metabolized benzodiazepines (e.g., midazolam, diazepam) via competitive metabolism through CYP3A4	Monitor for over-sedation and respiratory depression; conscious sedation protocol should consider a less aggressive titration protocol compared with other procedural areas
Benzodiazepines and non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil)	Prevents metabolism of oxidatively metabolized benzodiazepines (e.g., midazolam, diazepam) via inhibition of CYP3A4	
Opiates and statins	Prevents metabolism of opiates via competitive metabolism through CYP3A4	
Opiates and non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil)	Prevents metabolism of opiates via inhibition of CYP3A4	

ACS = acute coronary syndromes; cath = catheterization; COX = cyclooxygenase; INR = International Normalized Ratio; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

might make this option less attractive.

CCBs. Non-DHP CCBs, described previously, are well-known CYP3A4 inhibitors, which might increase CYP3A4-metabolized statin concentrations (atorvastatin, lovastatin, simvastatin). Additionally, many DHP CCBs (e.g., amlodipine, nifedipine) are competitively metabolized through CYP3A4. Several pharmacokinetic studies of co-administration have been performed specifically with diltiazem, where the AUC was increased by 4.8-fold with simvastatin (85) and 3- to 4-fold with lovastatin (86). Additionally, case reports of rhabdomyolysis have been published with diltiazem and simvastatin (87) as well as atorvastatin (88). In 2011, the FDA, presumably through an excess of severe adverse events identified through post-market surveillance, recommended a maximum dose of 10 mg/day of simvastatin when used with diltiazem or verapamil and a maximum of 20 mg/day when used with amlodipine (84). The significance of the interaction between amlodipine and simvastatin is not clear. A randomized crossover study by Nishio et al. (89) identified a 21% increase in the AUC of simvastatin when co-administered with amlodipine. However, in typical drug regimens these administrations are separate, with amlodipine given in the morning and simvastatin at nighttime. Park et al. (90) identified no significant change in the AUC of simvastatin in a crossover study when doses were separated by 4 h. Recommendations for other CYP3A4-metabolized statins (atorvastatin, lovastatin) are not provided.

OTHERS. Other strong CYP3A4 inhibitors are likely to increase concentrations of statins metabolized through this isoenzyme, including atorvastatin, lovastatin, and simvastatin. In particular, the mitigation of muscle-related toxicities with simvastatin has received a significant amount of attention from regulatory agencies. In 2011, the FDA communicated specific dose limitation recommendations for the use of simvastatin with many CYP3A4 inhibitors (84). In addition to the recommendations discussed in the preceding text with regard to fibrates and CCBs, these include a maximum of 20 mg/day of simvastatin when used with amiodarone or ranolazine and that the use of simvastatin is contraindicated with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, protease inhibitors, nefazodone, cyclosporine, and danazol. These recommendations were the result of an analysis of muscle-related toxicities in the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial and the FDA internal adverse effects reporting database (91). The risks associated with these medications and other CYP3A4 eliminated statins (atorvastatin, lovastatin) are less clear, but caution should be ascribed to the use of high-dose statins and strong CYP3A4 inhibitors. Another communication was provided by the FDA in 2012, where specific recommendations were provided for either maximum doses or contraindications for all CYP3A4-eliminated statins and many drug regimens used for human immunodeficiency virus or hepatitis C (92). Any patient with human immunodeficiency virus or hepatitis C who requires statin-based therapy should have a careful assessment of the potential for DDI before therapy initiation. The use of non-CYP3A4 eliminated statins (pitavastatin, pravastatin, or rosuvastatin) might be considered preferential agents in these populations.

Conclusions

The potential for meaningful DDI to occur among interventional cardiology patients is high and increasing. Such drug interactions can have devastating consequences, both in terms of jeopardizing acute procedural success and also adding increased risk for adverse events over the duration of treatment. Anticoagulant mixing, for example, might lead to an increase in bleeding complications related to the procedure. Furthermore, the variety of potential interactions with thienopyridine antiplatelets is concerning, because these drugs are vital to immediate and extended interventional success. Table 3 summarizes significant DDI that

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 12, 2012
DECEMBER 2012:1195–208

occur in the periprocedural setting pertinent to cardiac catheterization.

Although some DDI have the potential to induce harm in patients, many others are theoretical or exist only in pharmacokinetic form, with post-marketing registry reports as the "clinical evidence" to support the relevance of the issue. Given the pervasiveness of cardiovascular disease and its associated pharmacotherapy, more support from regulatory and scientific bodies is needed to more systematically examine the clinical relevance of potentially critical DDI among cardiovascular patients, particularly when such interactions might "innocently" occur because of over-the-counter medications (e.g., aspirin–NSAIDs or clopidogrel–omeprazole). It is believable that medication complexity will increase, and with that in mind, regulatory agencies and medical societies will need to steadily increase efforts to have expert-level review and evidence-based reports of clinically relevant DDI. Regardless of these actions, interventional providers need to be aware of the potential for DDI and associated harm in cardiovascular patients and of the appropriate action to take, if any, to minimize the potential for medication-related adverse events.

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REFERENCES

1. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008; 300:2867–78.
2. Solberg LI, Hurley JS, Roberts MH, et al. Measuring patient safety in ambulatory care: potential for identifying medical group drug-drug interaction rates using claims data. Am J Manag Care 2004;10:753–9.
3. Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. Drug Saf 2002;25:467–71.
4. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 2007;41:674–80.
5. Faxon DP, Eikelboom JW, Berger PB, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. Circ Cardiovasc Interv 2011;4:522–34.
6. Aggarwal A, Dai D, Rumsfeld JS, Klein LW, Roe MT. Impact of home warfarin use on the treatment and outcomes of patients undergoing percutaneous coronary intervention. Am J Cardiol 2008; 101:1413–7.
7. Wang TY, Chen AY, Peterson ED, et al. Impact of home warfarin use on treatment patterns and bleeding complications for patients with non-ST-segment elevation acute coronary syndromes: observations from the CRUSADE quality improvement initiative. Eur Heart J 2008;29:1103–9.
8. Bashore TM, Balter S, Barac A, et al. American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update. A report of the American College of Cardiology Foundation Task Force on Expert Consensus documents. J Am Coll Cardiol 2012;59:2221–305.
9. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19.
10. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292:45–54.
11. Cohen M, Mahaffey KW, Pieper K, et al. A subgroup analysis of the impact of prerandomization antithrombin therapy on outcomes in the SYNERGY trial: enoxaparin versus unfractionated heparin in non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2006;48:1346–54.
12. Drouet L, Bal dit Sollier C, Martin J. Adding intravenous unfractionated heparin to standard enoxaparin causes excessive anticoagulation not detected by activated clotting time: results of the STACK-on to ENOXaparin, (STACKENOX) study. Am Heart J 2009;158:177–84.
13. White HD, Chew DP, Hoekstra JW, et al. Safety and efficacy of switching from either unfractionated heparin or enoxaparin to bivalirudin in patients with non-ST-segment elevation acute coronary syndromes managed with an invasive strategy: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol 2008;51:1734–41.
14. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354: 1464–76.
15. Wright RS, Anderson JL, Adams CD, et al. ACCF/AHA focused update incorporated into the 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 Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, society for cardiovascular angiography and interventions, and the society of thoracic surgeons. J Am Coll Cardiol 2011; 57:e215–367.
16. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J 2006;27:519–26.
17. Mattichak SJ, Reed PS, Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction. J Interv Cardiol 2005;18:163–6.
18. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. J Invasive Cardiol 2006;18: 162–4.
19. Rogacka R, Chieffo A, Michev I, et al. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. J Am Coll Cardiol Intv 2008;1: 56–61.
20. Nguyen MC, Lim YL, Walton A, et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? Eur Heart J 2007;28:1717–22.
21. Holmes DR Jr., Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. J Am Coll Cardiol 2009;54:95–109.
22. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809–17.
23. Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther 2006;80:264–74.
24. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361:573–4.
25. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115:1634–42.
26. Food and Drug Administration. Information for healthcare professionals: concomitant use of ibuprofen and aspirin. Available at: http://

www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm. Accessed October 3, 2012.
27. Meek IL, Vonkeman HE, Kasemier J, Movig KL, van de Laar MA. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. Eur J Clin Pharmacol 2012 Aug 14 [E-pub ahead of print].
28. Schuijt MP, Huntjens-Fleuren HW, de Metz M, Vollaard EJ. The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. Br J Pharmacol 2009;157:931–4.
29. Gladding PA, Webster MW, Farrell HB, Zeng IS, Park R, Ruijne N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol 2008;101:1060–3.
30. Mullangi R, Srinivas NR. Clopidogrel: review of bioanalytical methods, pharmacokinetics/pharmacodynamics, and update on recent trends in drug-drug interaction studies. Biomed Chromatogr 2009;23:26–41.
31. Rehmel JL, Eckstein JA, Farid NA, et al. Interactions of two major metabolites of prasugrel, a thienopyridine antiplatelet agent, with the cytochromes P450. Drug Metab Dispos 2006;34:600–7.
32. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008;52:1502–17.
33. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009;101:714–9.
34. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009;157:148.e1,148.e5.
35. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;374:989–97.
36. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008;51:256–60.
37. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937–44.
38. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713–8.
39. Kreutz RP, Stanek EJ, Aubert R, et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study. Pharmacotherapy 2010;30:787–96.
40. Simon T, Steg PG, Gilard M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French registry of acute ST-Elevation and non-ST-Elevation myocardial infarction (FAST-MI) registry. Circulation 2011;123:474–82.
41. Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med 2010;152:337–45.
42. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909–17.
43. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;56:2051–66.
44. Food and Drug Administration. Information for healthcare professionals: update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm. Accessed October 3, 2012.
45. Beaird SL. HMG-CoA reductase inhibitors: assessing differences in drug interactions and safety profiles. J Am Pharm Assoc (Wash) 2000;40:637–44.
46. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. Circulation 2003;107:32–7.
47. Mitsios JV, Papathanasiou AI, Rodis FI, Elisaf M, Goudevenos JA, Tselepis AD. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is administered concomitantly for 5 weeks in patients with acute coronary syndromes. Circulation 2004;109:1335–8.
48. Wenaweser P, Windecker S, Billinger M, et al. Effect of atorvastatin and pravastatin on platelet inhibition by aspirin and clopidogrel treatment in patients with coronary stent thrombosis. Am J Cardiol 2007;99:353–6.
49. Geisler T, Zürn C, Paterok M, et al. Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy. Eur Heart J 2008;29:1635–43.
50. Müller I, Besta F, Schulz C, Li Z, Massberg S, Gawaz M. Effects of statins on platelet inhibition by a high loading dose of clopidogrel. Circulation 2003;108:2195–7.
51. Serebruany VL, Malinin AI, Callahan KP, Gurbel PA, Steinhubl SR. Statins do not affect platelet inhibition with clopidogrel during coronary stenting. Atherosclerosis 2001;159:239–41.
52. Saw J, Steinhubl SR, Berger PB, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. Circulation 2003;108:921–4.
53. Saw J, Brennan DM, Steinhubl SR, et al. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. J Am Coll Cardiol 2007;50:291–5.
54. Lotfi A, Schweiger MJ, Giugliano GR, Murphy SA, Cannon CP, TIMI 22 Investigators. High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients—a Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) analysis. Am Heart J 2008;155:954–8.
55. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. J Am Coll Cardiol 2008;52:1557–63.
56. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Calcium-channel blockers decrease clopidogrel-mediated platelet inhibition. Heart 2010;96:186–9.
57. Good CW, Steinhubl SR, Brennan DM, Lincoff AM, Topol EJ, Berger PB. Is there a clinically significant interaction between calcium channel antagonists and clopidogrel?: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Circ Cardiovasc Interv 2012;5:77–81.
58. Dvorak Z. Drug-drug interactions by azole antifungals: beyond a dogma of CYP3A4 enzyme activity inhibition. Toxicol Lett 2011;202:129–32.
59. Lazar JD, Hilligoss DM. The clinical pharmacology of fluconazole. Semin Oncol 1990;17:14–8.
60. Farid NA, Payne CD, Small DS, et al. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. Clin Pharmacol Ther 2007;81:735–41.
61. Sibbing D, von Beckerath N, Morath T, et al. Oral anticoagulation with coumarin derivatives and antiplatelet effects of clopidogrel. Eur Heart J 2010;31:1205–11.
62. Brilinta. (package insert) Wilmington, Delaware: AstraZeneca, LP, 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022433s000lbl.pdf.
63. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the platelet inhibition and patient outcomes (PLATO) trial. Circulation 2011;124:544–54.

64. Serebruany VL. Aspirin dose and ticagrelor benefit in PLATO: fact or fiction? Cardiology 2010;117:280–3.
65. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002; 96:1004–17.
66. Bailey PL, Pace NL, Ashburn MA, Moll JW, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 1990;73:826–30.
67. Tanaka E. Clinically significant pharmacokinetic drug interactions with benzodiazepines. J Clin Pharm Ther 1999;24:347–55.
68. McDonnell CG, Harte S, O'Driscoll J, O'Loughlin C, Van Pelt FN, Shorten GD. The effects of concurrent atorvastatin therapy on the pharmacokinetics of intravenous midazolam. Anaesthesia 2003;58: 899–904.
69. Backman JT, Olkkola KT, Aranko K, Himberg JJ, Neuvonen PJ. Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol 1994;37:221–5.
70. Ahonen J, Olkkola KT, Salmenperä M, Hynynen M, Neuvonen PJ. Effect of diltiazem on midazolam and alfentanil disposition in patients undergoing coronary artery bypass grafting. Anesthesiology 1996;85: 1246–52.
71. Armstrong SC, Wynn GH, Sandson NB. Pharmacokinetic drug interactions of synthetic opiate analgesics. Psychosomatics 2009;50: 169–76.
72. Levin TT, Bakr MH, Nikolova T. Case report: delirium due to a diltiazem-fentanyl CYP3A4 drug interaction. Gen Hosp Psychiatry 2010;32:648.e9–10.
73. Shitara Y, Hirano M, Sato H, Sugiyama Y. Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2 (OATP2/OATP1B1:SLC21A6)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. J Pharmacol Exp Ther 2004;311: 228–36.
74. Backman JT, Kyrklund C, Kivistö KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. Clin Pharmacol Ther 2000;68:122–9.
75. Whitfield LR, Porcari AR, Alvey C, Abel R, Bullen W, Hartman D. Effect of gemfibrozil and fenofibrate on the pharmacokinetics of atorvastatin. J Clin Pharmacol 2011;51:378–88.
76. Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther 2004;75:455–63.
77. van Puijenbroek EP, Du Buf-Vereijken PW, Spooren PF, van Doormaal JJ. Possible increased risk of rhabdomyolysis during concomitant use of simvastatin and gemfibrozil. J Intern Med 1996;240:403–4.
78. Tal A, Rajeshawari M, Isley W. Rhabdomyolysis associated with simvastatin-gemfibrozil therapy. South Med J 1997;90:546–7.
79. Duell PB, Connor WE, Illingworth DR. Rhabdomyolysis after taking atorvastatin with gemfibrozil. Am J Cardiol 1998;81:368–9.
80. Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA Reductase inhibitors and gemfibrozil combination therapy. Pharmacoepidemiol Drug Saf 2004;13:417–26.
81. McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clin Epidemiol 2007;60: 812–8.
82. Crestor [package insert]. Wilmington, Delaware: AztraZeneca Pharmaceuticals, LP, 2010. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s021lbl.pdf.
83. Mevacor [package insert]. Etobicoke, Ontario, Canada: Mylan Pharmaceuticals, 2010.
84. Food and Drug Administration. FDA Drug Safety Communication: new restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm. Accessed October 3, 2012.
85. Mousa O, Brater DC, Sunblad KJ, Hall SD. The interaction of diltiazem with simvastatin. Clin Pharmacol Ther 2000;67:267–74.
86. Azie NE, Brater DC, Becker PA, Jones DR, Hall SD. The interaction of diltiazem with lovastatin and pravastatin. Clin Pharmacol Ther 1998;64:369–77.
87. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. Nephron 2001;89:117–8.
88. Lewin JJ III, Nappi JM, Taylor MH. Rhabdomyolysis with concurrent atorvastatin and diltiazem. Ann Pharmacother 2002;36:1546–9.
89. Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res 2005;28: 223–7.
90. Park CG, Lee H, Choi JW, Lee SJ, Kim SH, Lim HE. Non-concurrent dosing attenuates the pharmacokinetic interaction between amlodipine and simvastatin. Int J Clin Pharmacol Ther 2010;48: 497–503.
91. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010;376: 1658–69.
92. Food and Drug Administration. FDA Drug Safety Communication: interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm. Accessed October 3, 2012.

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