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HEALTH POLICY STATEMENT

ACCF/AHA 2011 Health Policy Statement on Therapeutic Interchange and Substitution

A Report of the American College of Cardiology Foundation Clinical Quality Committee

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This document was approved by the American College of Cardiology Foundation (ACCF) Board of Trustees in June 2011 and the American Heart Association (AHA) Science Advisory and Coordinating Committee in May 2011. For the purpose of complete transparency, disclosure information for the ACCF Board of Trustees, the board of the convening organization of this document, is available at: http://www.cardiosource.org/ACC/About-ACC/Leadership/Officers-and-Trustees.aspx. ACCF board members who have relationships with industry and other entities that are relevant to the document may review and comment on the document but may not vote on approval.

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Preamble

This document is an American College of Cardiology Foundation (ACCF) health policy statement and is intended to promote or advocate a position, be informational in nature, and offer guidance to the stakeholder community regarding the ACCF's stance on healthcare policies and programs. Health policy statements are not intended to offer clinical guidance and do not contradict existing ACCF clinical policy. They are overseen by the ACCF Clinical Quality Committee (CQC), the group responsible for developing and implementing all health policy statement policies and procedures related to topic selection, commissioning writing committees, and defining document development methodologies. The CQC brings together various areas of the College such as the Advocacy Committee, the National Cardiovascular Data Registry, the ACCF/AHA (American Heart Association) Task Forces on Guidelines and Performance Measurement, and the ACCF Appropriate Use Criteria Steering Committee. The CQC recommended the development of this health policy statement to update the ACCF's official position on therapeutic substitution.

To avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. The CQC reviews these disclosures to determine what companies make products (on market or in development) that pertain to the document under development. Based on this information, a writing committee is formed to include a majority of members with no *relevant* relationships with industry and other entities (RWI), led by a chair with no *relevant* RWI. Authors with *relevant* RWI are not permitted to draft or vote on text or recommendations pertaining to their RWI. RWI is reviewed on all conference calls and updated as changes occur. Author and peer reviewer RWI pertinent to this document are disclosed in Appendixes 1 and 2, respectively. In addition, to ensure complete transparency, authors' *comprehensive disclosure information*—including RWI not pertinent to this document—is available as an online supplement to this document. Disclosure information for the ACCF CQC is also available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx, as well as the ACCF disclosure policy for document development at www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

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Joseph P. Drozda, Jr., MD, FACC
Chair, ACCF Clinical Quality Committee

1. Introduction

1.1. Purpose of This Document

Therapeutic interchange/substitution has been defined as the dispensation of drugs alternative to those that have been specifically prescribed. These alternative drugs may be either generic drugs or drugs that are similar, albeit not identical. These drugs may also be chemically different with different pharmacokinetic properties but which are believed to be therapeutically similar.

The concepts of therapeutic interchange and substitution have received increasing attention. One of the most common reasons is the development of multiple drugs in a similar class, for example, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, statins, or calcium channel blockers. A second group of common reasons is the development of slightly differing drugs within the same class. Perhaps the most important driving issues are economic. As healthcare costs rise inexorably and the limits of patent protections are either exceeded, circumvented, or ignored worldwide, generic drugs and devices are often developed and marketed under the understanding that they provide the same benefit and safety but with greatly reduced costs. These issues are all central to the concepts of therapeutic interchange and substitution and are the focus of this health policy statement.

This document is meant to stimulate discussion of the following issues and highlight the controversies that surround this increasingly widely used strategy of care that can have far-reaching implications.

1. What is therapeutic interchange/substitution?
2. Do state, national, and international regulatory agencies control the process?
3. Can therapeutic interchange/substitution occur without physician knowledge?
4. Is there a difference between drugs and biologics in terms of therapeutic interchange/substitution?
5. Are generics really equivalent?
6. Does the burgeoning field of pharmacogenomics affect therapeutic interchange/substitution?
7. Are there specific patient groups who are at increased risk with therapeutic interchange/substitution?
8. How do we address the conflict between evidence-based data and economic pressures?
9. How does the ACCF/AHA guideline process address the issue of drug class versus specific agent?

1.2. Document Development Process

The writing committee included ACCF and AHA members representing general cardiology, geriatric cardiology, pediatric cardiology, neurology, critical care, and clinical pharmacology who met the College's disclosure requirements as described in the Preamble. The committee convened its work by conference call and e-mail to finalize the document outline, develop the initial draft, revise the draft based on committee feedback, and ultimately sign off on the document for external peer review. Peer review consisted of 13 reviewers representing 173 comments. Comments were reviewed and addressed by the writing committee. A CQC liaison served as lead reviewer to ensure that all comments were addressed adequately. Both the writing committee and CQC approved the final document to be sent for board review. The AHA Science Advisory and Coordinating Committee and the ACCF Board of Trustees reviewed the document, including all peer review comments and writing committee responses, and approved the document in May and June 2011, respectively. The document is considered current until the CQC revises it or withdraws it from publication.

1.3. Definitions, Terminology, and Regulations

When approaching the clinical and legal complexity surrounding generic substitution and therapeutic interchange, healthcare providers must be well versed in the terminology used by the U.S. Food and Drug Administration (FDA), the generics approval process, and the current regulatory issues surrounding bioequivalence. See Table 1 for the key terms and definitions used in this document.

1.3.1. Terminology

All prescription and over-the-counter generic medications must meet the standards established by the FDA, which were initially proposed under the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-

Table 1. Key Terms and Definitions Related to Therapeutic Interchange/Substitution

Term	Definition
Bioavailability	The rate and extent to which a drug's active ingredient is absorbed from the drug product and becomes available at its site of action.
Bioequivalence	The absence of a significant difference in bioavailability between a drug product and its innovator when administered at the same molar dose under similar conditions in an appropriately designed study.
Biologics	Biological agents that are derived from living sources such as cultures of bacteria, viruses, or human or animal tissue and may have either a therapeutic or diagnostic intent.
Biosimilars	"Generic" biologics that are copies of a therapeutic protein, not manufactured by an innovator company, and approved through an abbreviated process.
Critical dose drugs	Drugs in which comparatively small differences in dose or concentration may lead to serious therapeutic failures and/or serious drug reactions.
Generic substitution	The act of switching between a branded drug and its therapeutically equivalent generic version.
Narrow therapeutic index drugs	Drugs identified as having less than a 2-fold difference between the median lethal and the median effective dose, having less than a 2-fold difference between the minimum toxic and minimum effective concentrations in the blood, and where safe and effective use of the drug requires careful titration and patient monitoring.
Orange Book (i.e., *Approved Drug Products with Therapeutic Equivalence Evaluations*)	An FDA publication that identifies drug products approved on the basis of safety and effectiveness. It contains information as to whether generic versions of medications are considered to be therapeutic equivalents to the drugs manufactured by the innovator company (1).
Pharmaceutical equivalents	Drug products that contain the identical amounts of the same active ingredient in the same dosage form and route of administration, as well as meet compendia or other applicable standards of strength, quality, purity, and identity.
Reference innovator	The initially FDA-approved drug in this category.
Therapeutic equivalent	Drug products that are approved as safe and efficacious; are pharmaceutical equivalents; are bioequivalent; and are manufactured in compliance with current Good Manufacturing Practice regulations.
Therapeutic interchange	The act of dispensing, with the authorization of the initial prescriber, an alternative drug that is believed to be therapeutically similar but may be chemically different, in a different category, with different pharmacokinetic properties. This interchange is based on the premise that the substituted drug will provide a similar clinical efficacy, desired outcome, and safety profile.
Therapeutic substitution	The act of therapeutic interchange that occurs without the prior authorization of the initial prescriber.

FDA indicates U.S. Food and Drug Administration.

Waxman Amendment") (2). When the FDA approves a new generic product, it concludes and ratifies that the generic is therapeutically equivalent to its corresponding reference innovator product. The generic product can therefore be substituted at the time of dispensing for the reference innovator or brand-name product on the expectation that the generic will produce the identical clinical response with a similar safety profile. The FDA classifies products as therapeutically equivalent when they are approved as safe and efficacious, are pharmaceutical equivalents, are bioequivalent, and are manufactured in compliance with current Good Manufacturing Practice regulations (1).

Drug products are considered pharmaceutical equivalents if they contain the identical amounts of the same active ingredient in the same dosage form and route of administration, as well as meet compendia or other applicable standards of strength, quality, purity, and identity. However, generic medications may differ from the innovator product in shape, drug release mechanisms, scoring configurations, and shelf lives/expiration times (1). Standards of pharmaceutical equivalence do not require that additives such as fillers, coatings, flavoring, coloring, and binders utilized in generic formulations be similar or identical to the innovator counterparts. It is important to note that some additives traditionally thought to be inert, such as alcohol sugars, cyclodextrans, and polysorbate-80, may alter a drug's dissolution, thereby impacting its bioavailability (3–5).

The FDA defines *bioequivalence* as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action (or bioavailability) when administered at the same molar dose under similar conditions in an appropriately designed study (1). In other words, if the innovator and generic drugs are bioequivalent, then they should exhibit equivalent drug concentration-time profiles in the blood (6).

1.3.2. Generics

When submitting an Abbreviated New Drug Application for a generic drug, a manufacturer must submit ≥1 bioequivalence studies in which subjects are administered the generic and innovator products, and drug blood concentrations are measured to determine the maximum drug concentration (Cmax) and total drug exposure (area under the curve [AUC]) (7,8). These studies typically consist of 12 to 36 healthy male and female volunteers using the highest strength of a drug's product line and can be either single-dose crossover or multidose steady-state studies. When evaluating bioequivalence parameter results, 2 one-sided bioequivalence tests may be performed (6,9). One test verifies that the bioavailability of the generic is not >20% less than that of the innovator product, whereas the other confirms the bioavailability of the innovator product is not >20% less than the generic product (6,9). The use of this "20% rule" is based on a decision by FDA medical experts who suggest that for most drugs, a ±20% difference in the active ingredients' blood concentrations is not clinically significant (1). For the 2 products to be deemed bioequivalent, the 90% confidence interval of the geometric mean of the ratio of the generic compared with the innovator product of the Cmax and AUC values must lie between 80% and 125% (6,8) (see Figure 1).

Therefore, the established bioequivalence limits are 80% to 125%. Once approved, a generic product is assigned a therapeutic rating and is listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluation*, also referred to as the *Orange Book* (1). Therapeutically equivalent drugs are assigned either an A rating or AB rating. Table 2 summarizes the FDA coding system for therapeutic equivalence for drug products.

1.3.3. Bioequivalence

Over the past decade, many issues have arisen that have tested the FDA's current bioequivalence criteria, particularly as they relate to narrow therapeutic index and critical dose drugs as

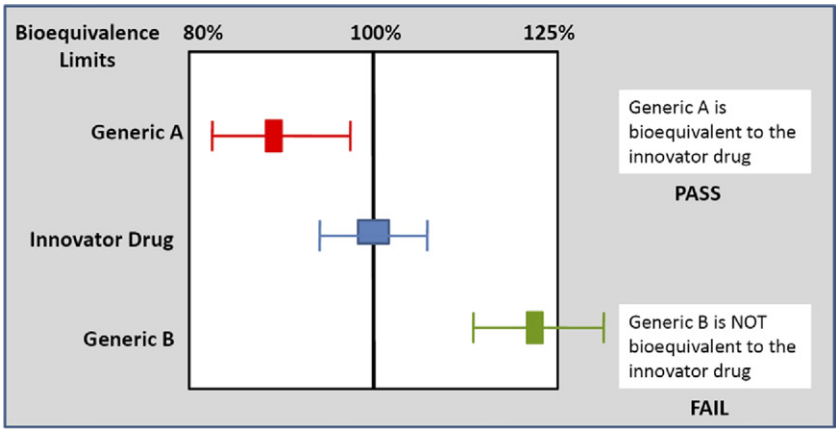

Figure 1. Diagram Illustrating Possible Bioequivalence Study Outcomes

Table 2. FDA Coding System for Therapeutic Equivalence for Drug Products

Code	Description
A	Drug products that the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, that is, drugs for which: • There are no known or suspected bioequivalence problems. These are designated AA (conventional dosage forms), AN (solutions and powders for aerosolization), AO (injectable oil solutions), AP (injectable aqueous solutions), or AT (topical products) • Actual or potential bioequivalence problems have been resolved with adequate in vitro and/or in vivo evidence supporting bioequivalence. These are designated AB.* Drugs coded as AB under a specific product heading are considered to be therapeutically equivalent only to other drugs coded as AB under that heading.
B	Drug products that the FDA at this time considers not to be therapeutically equivalent to the other pharmaceutically equivalent products for which 1 of the following is true: • Actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than the active ingredients. • The quality standards are inadequate, or the FDA has had an insufficient basis to determine therapeutic equivalence. • The drug products are currently under regulatory review. The subcodes consist of BC (extended-release capsules, injectables, tablets); BD (active ingredients and dosage forms with documented bioequivalence problems); BE (delayed release oral dosage forms); BN (aerosol-nebulizer drug delivery); BP (active ingredients and dosage forms with potential bioequivalence problems); BR (suppositories and enemas); BS (products having drug standard deficiencies); BT (topical products); BX (drug products with insufficient data); or B†.

*A number is added to the end of the code (e.g., AB1, AB2), which indicates that >1 reference drug of the same strength has been designated under the same heading. Two or more reference medications are identified only when there are at least 2 potential reference drug products that are not bioequivalent to each other. †Code B represents drugs that may have been previously assigned an A or B code before new information raising significant questions about therapeutic equivalence was received by the FDA. The therapeutic equivalence of the product may be redetermined after the FDA completes its investigation and review.

FDA indicates U.S. Food and Drug Administration.

Table content adapted from U.S. Food and Drug Administration (1).

well as biologics and biosimilars. A critical issue is highlighted in the field of heart failure relating to the fixed-dose combination of hydralazine/isosorbide dinitrate (as studied in A-HeFT [African-American Heart Failure Trial]) versus generic hydralazine and generic nitrates. This has great implications because of the lack of bioequivalence between the different formulations of isosorbide dinitrate and hydralazine (10).

The issue of bioequivalence also has significant clinical impact specifically related to narrow therapeutic index drugs. These drugs are identified as those having less than a 2-fold difference between the median lethal and the median effective dose, having less than a 2-fold difference between the minimum toxic and minimum effective concentrations in the blood, and where safe and effective use of the drug requires careful titration and patient monitoring (11). The critical dose drugs are those drugs in which comparatively small differences in dose or concentration may lead to serious therapeutic failures and/or serious drug reactions (11). The impact of this imprecision in defining the parameters of a narrow therapeutic index and critical dosing medication schedules is important but difficult to measure. The FDA does not formally designate specific critical dose and narrow therapeutic index drug clarifications; however, possible examples would include certain antiepileptics, antiarrhythmics, thyroid preparations, immunosuppressants, and anticoagulants (Table 3). Additionally, many healthcare providers, scientists, and regulatory agencies have expressed alarm that bioequivalent generic and brand-name critical dose and narrow therapeutic index drugs may not be equivalent in their effects on various clinical parameters. Concern also exists regarding the potential for generic-to-generic switches with these drugs as bioequivalence assessments required by the FDA compare each generic to its innovator product. Generics are not compared with each other. Finally, bioequivalence studies are not always published in the literature and may be difficult to obtain.

In April 2010, the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology evaluated these concerns and recommended that critical dose/narrow therapeutic index drugs are a distinct group of products; the FDA should develop a list of critical dose/narrow therapeutic index drugs; and the current bioequivalence standards are not sufficient for these drugs (12).

Additional evaluation of bioequivalence may involve measurement of pharmacodynamic effects. These may include, for example, measuring platelet aggregation. The linkage between pharmacodynamic effects and clinical outcomes remains uncertain (13). It must also be remembered that current methods of determining bioequivalence and therapeutic equivalence do not account for pharmacokinetic variation. Better knowledge of pharmacokinetic variation has significant consequences for current federal regulations and state laws regulating therapeutic substitution.

1.3.4. Biologics and Biosimilars

As patents for several biologic products manufactured using recombinant DNA technology are nearing expiration, the issue of "generic" biologic interchange will need to be addressed

Table 3. Examples of Narrow Therapeutic Index Drugs

Therapeutic Class	Examples
Antiarrhythmic drugs	Digoxin, disopyramide, flecainide, procainamide, quinidine
Anticoagulant drugs	Warfarin
Antiepileptic drugs	Carbamazepine, oxcarbazepine, phenytoin, valproic acid
Antirejection drugs	Cyclosporine, everolimus (Afinitor), sirolimus (Rapamune), tacrolimus
Bronchodilators	Theophylline
Mood stabilizers	Lithium
Synthetic hormones	Ethinyl estradiol, levothyroxine

(14). According to the U.S. Code of Federal Regulations, a biologic is "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man" (15, p. 6). Biologics are derived from living sources such as cultures of bacteria, viruses, or human or animal tissue and may have either a therapeutic or diagnostic intent. Examples of classes of biologics consist of recombinant or purified proteins such as cytokines and thrombolytic agents, erythropoietin, human growth hormone, monoclonal antibodies, blood derivatives, insulin, and vaccines (16). Biopharmaceuticals differ from traditional small molecule drugs in that they exhibit a high molecular weight with a complex 3-dimensional structure, rely on a complex manufacturing processes, are produced from living organisms and are often heterogeneous, and demonstrate significant immunogenic safety issues (17,18). Additionally, these agents are difficult to characterize completely by physicochemical analytical methods or bioassays, and their biological activity is highly dependent on the reproducibility of the production process, manufacturing standards, and maintaining cold chain integrity (17). Biosimilars, also known as biogenerics, post-patent biologics, and follow-on biologicals, are considered biologic agents that are copies of a therapeutic protein, not manufactured by an innovator company, and approved through an abbreviated process (19).

Whereas traditional small molecule drugs are approved under the Food, Drug, and Cosmetic Act, most biologics are approved under the Public Health Service Act (PHSA) (20); thus, the regulations from the Hatch-Waxman Amendment do not apply to biologics. Therefore, issues such as bioequivalence and interchangeability as well as innovator exclusivity periods were initially not addressed. As a part of healthcare reform, the Biologics Price Competition and Innovation Act was passed in 2009, amending the PHSA with issues of biosimilars or biosimilarity. This act defines *biosimilarity* as present when: 1) the biological product is "highly similar to the reference product, notwithstanding minor differences in clinically inactive components"; and 2) "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" (21, p. 61498). When approving a biosimilar product, the FDA requires data from analytical, animal, and clinical studies documenting similarity in safety, purity, and potency; mechanism of action; prescribing conditions; and route of administration between the biological product and the reference product. Interchangeability can occur only when the biologic product: 1) is considered a biosimilar to the reference product; and 2) can be expected to produce the same clinical results as the reference product in any given patient (21). Additionally, for a product that requires multiple administrations in the same individual, "the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and reference product is not greater than the risk of using the reference product without such alternation or switch" (21, p. 61498). It is important to acknowledge, however, that biosimilars do not require demonstration of efficacy and safety in clinical outcome trials; whether meaningful differences may exist regarding impact on clinical outcomes is uncertain.

An example of the controversy of biosimilars specific to patients with cardiovascular disease is the approval of the first generic low-molecular-weight heparin (LMWH) enoxaparin in July 2010. In 2008, the FDA recalled several batches of heparin as a result of increased prevalence of death from anaphylactoid-type reactions secondary to contaminated heparin from over-sulfated chondroitin sulfates (OSCS), high-molecular-weight dermatan sulfate, and heparin sulfate (22). Because LMWHs are produced using heparin, OSCS have been detected in batches of LMWHs (22). Additionally, although generic LMWHs may demonstrate acceptable molecular weight and anti-Xa profiles, they can exhibit assay-based differences and immunogenicity profiles. With these safety issues in mind, as new biosimilars appear on the market, close pharmacovigilance should be considered to completely characterize the drug risk profile.

2. Pharmacogenomics

With the completion of the Human Genome Project, advances in DNA sequencing and genotyping have made it possible to rapidly and accurately identify variation in DNA sequence and structure. Correlation between genomic variation and drug response has allowed for better prediction of individual responses to specific drugs, optimization for drug selection and dose, and avoidance of potential medication misadventures (23). Although used interchangeably, the terms *pharmacogenetics* and *pharmacogenomics* are different. Pharmacogenetics is the analysis of candidate genes to evaluate the relationship between individual genes and drug effects, whereas pharmacogenomics is the study of the relationship between variants in a large collection of genes across the entire genome to find genetic variation that correlates with drug response (23). In the past, progress in the field of pharmacogenetics has been hindered by many social, regulatory, financial, and logistic obstacles. Fortunately, many of these barriers are rapidly disappearing. Presently, genomic testing has begun to move from the bench to the bedside. For example, chemotherapy decisions using biologic agents such as trastuzumab (Herceptin) and cetuximab (Erbitux) are based on testing for the human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR), respectively (17). The commonly used drug warfarin can be monitored using the international normalized ratio (INR). Dosing can be personalized using genotype data from the cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes (24,25). Using this genotype data may facilitate selection of the optimal dose chosen during initiation of warfarin therapy rather than relying completely on frequent measurement of INR, which can be both inconvenient and costly. CYP genotyping can also be used for selection and monitoring of other drugs, such as antidepressants (26).

Specifically addressing cardiovascular pharmacogenetics, evidence has suggested that inheritance may contribute to variation in response for drugs used to treat hypertension and heart failure within and across therapeutic classes. In the INVEST-GENES (International Verapamil SR-Trandolapril Study Genetic) study, polymorphisms in CYP3A5 influenced response to verapamil in blacks and Hispanics, where the carrier status of the 2 functional alleles is common (27). The investigators also determined that white patients with hypertension and coronary artery disease with the single nucleotide polymorphism (SNP) (rs2357928) in the *CACNB2* gene receiving sustained release verapamil had a significantly increased risk for the first occurrence of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke compared with those receiving the beta-blocker atenolol (28). Beta blockers in heart failure provide important lessons regarding class effects. Two formulations of the same drug—metoprolol tartrate and metoprolol succinate—have very different levels of evidence for improving outcome in chronic heart failure, with metoprolol succinate having strong evidence for a major survival benefit (29), whereas metoprolol tartrate at a different dose is significantly inferior to the effective carvedilol (30). Contrary to studies with carvedilol, metoprolol succinate, and bisoprolol in patients with heart failure, the BEST (Beta Blocker Evaluation of Survival Trial) failed to show a significant survival benefit for patients with systolic dysfunction treated with bucindolol, a fourth-generation beta blocker (31,32). When specifically analyzing polymorphisms in the beta-adrenergic receptor, data from the BEST Genetic substudy suggested that improvement in survival and reduction in hospitalization was noted only for patients treated with bucindolol who expressed the *Arg389Arg* genotype (33). In contrast, minimal benefit was apparent in patients either homozygous or heterozygous for the Gly389 allele. These results were not considered to be adequate for FDA approval for bucindolol for genetically determined populations. Moreover, these findings were in contrast to the genetic substudy of the MERIT-HF (Metoprolol Cr/XL Randomized Intervention Trial in Heart Failure) in which the Gly389 allele failed to confer a significant morbidity and mortality impact in heart failure patients receiving metoprolol succinate (34).

Similar issues also exist with other medications, including clopidogrel. Because clopidogrel is expected to be available as a generic within the next 2 years, many pharmacy benefit plans may wish to interchange more expensive antiplatelet agents currently being used, such as prasugrel, with the generic clopidogrel. However, patients with a polymorphism for CYP2C19, the enzyme responsible for conversion of clopidogrel (Plavix) to its active metabolite, could exhibit diminished platelet response to clopidogrel as well as higher rates of cardiovascular events after acute coronary syndrome and percutaneous coronary interventions independent of the clopidogrel dose (13,35,36). The role of genetic testing to guide thienopyridine use, however, is uncertain (13). In addition, these genomic issues have not been demonstrated with the novel ADP receptor antagonists, prasugrel (Effient), or ticagrelor (13,37,38).

Finally, cardiovascular pharmacogenomics data have been used to predict the risk for adverse events with statins. The genomewide association Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) found a strong correlation of myopathy with the rs4363657 SNP located within the *SLCO1B1* gene in patients receiving simvastatin 80 mg daily (39). The *SLCO1B1* gene encodes OATP1B1, the solute carrier organic transporter responsible for the active transport of statins into the hepatocyte. About 30% of the study population was either heterozygous or homozygous, whereas only 2% were homozygous for the variant allele. It has been estimated that the *SLCO1B1* variant could account for 60% of statin-induced myopathy cases in the population (39,40). Dosing of simvastatin should be individualized in patients who are either homozygous or heterozygous for this variant allele (40).

It has been estimated that by 2015, a physician may be able to provide a patient with his or her complete gene sequencing so as to direct drug therapy (41), although many challenges remain to generate the evidence needed to routinely use genetics to guide drug selection and dosing. As these genomic data become more readily available, pharmacists and providers may need to incorporate these data into their decision analysis when considering therapeutic interchange. These data are not only important from a potential cost-effective approach but also from the standpoint of patient safety. Based on the evidence presented, blindly interchanging within and across therapeutic classes when and if genomic data are available could result in poor clinical outcomes and potential adverse drug events.

3. Federal Regulations and State Laws

The FDA does not regulate generic substitution, therapeutic interchange, or therapeutic substitution and lacks authority to limit physician prescribing. The FDA's primary responsibility is updating information for healthcare providers, not controlling their decisions (42). On average, the retail price of a generic drug is 75% lower than the retail price of a brand-name drug (43). As a result, generic substitution rates in the United States are almost 90% of the prescriptions when there is a generic equivalent available (44). In every state, product substitutions must be made in accordance with the individual state's Pharmacy Practice Act (Appendix 3). As a result, there is variation in requirements for when pharmacists can or must dispense generics among states. In states with a positive formulary approach, a list of generic drug products from different manufacturers identifies the products that may be substituted for one another. Most states specify the *Orange Book* as the positive formulary (45). However, the FDA notes that the *Orange Book* is not an official, legally binding regulation. The FDA

explicitly states that the listing of drugs with therapeutic equivalency constitutes advice and does not mandate which drug products should be prescribed (1). In states with a negative formulary approach, drugs are listed for which substitution by another drug is not allowed. Such may be the case with narrow therapeutic index drugs. Although the FDA considers many narrow therapeutic index generics bioequivalent, some states require that generic versions cannot be substituted without the prescriber's consent (44). In North Carolina, narrow therapeutic index drugs are required to be refilled using only the same drug product last dispensed by the same manufacturer unless the prescriber is notified by the pharmacist prior to dispensing, and the prescriber and the patient give documented consent (46).

State laws also vary regarding how the final product selection is determined on the prescription. In the majority of states, prescribers must expressly indicate by writing directly on the prescription whether generic substitution is or is not permitted. Other states include preprinted wording on the prescription that must be signed or checked to prevent generic product substitution (47).

The practice of therapeutic interchange by pharmacists is also allowed in some states (44). Again, the laws regarding this practice vary widely from state to state, but in all cases, a preapproved protocol is required. Interchange protocols can be developed in both an institutional and outpatient setting as long as a functional formulary system is in place with an appropriate drug use–setting body.

Finally, the loss of control by individual physicians when formulary management determines drug choice has led to speculation that potential serious litigation could arise from professional activities associated with this practice. Despite this concern, there have been no successful lawsuits involving therapeutic interchange (42). In fact, when done appropriately, compliance with formulary guidelines set forth by an institutional pharmacy and therapeutics committee is a virtually impenetrable shield to liability (42).

4. Therapeutic Approaches

4.1. Therapeutic Interchange

Although the terms *therapeutic interchange* and therapeutic substitution have been used analogously in the literature, distinct differences do exist in clinical practice. Many pharmacy and medical organizations have addressed the issue of therapeutic interchange (48–53). Interchange can occur in which 1 drug is switched for another drug within the same therapeutic class (e.g., benazepril for lisinopril, or ranitidine for famotidine) or from different classes but with a similar pharmacological effect and potency (e.g., lisinopril for amlodipine). Environments where therapeutic interchange may occur are in the hospital setting and federal facilities in which an approved formulary system has been implemented, in situations where a collaborative drug management program between the pharmacist and provider has been established, or where a contractual arrangement has been made between a provider and pharmacy benefit plans.

When optimizing pharmacotherapy through therapeutic interchange, the approach should incorporate concepts of both patient-centered care and interprofessional collaboration. The Institute of Medicine defines *patient-centered care* as: "healthcare that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support they need to make decisions and participate in their own care" (54, p. 7). Health Canada expands on this definition to include interprofessional collaboration among healthcare team members. Their definition of collaborative patient-centered practice promotes the active participation of each healthcare discipline in patient care though enhancing patient and family-centered goals and values, providing mechanisms for continuous communication among caregivers, optimizing staff participation in clinical decision making within and across disciplines, and fostering respect for disciplinary contributions for all professionals (55). Depending on the environment, therapeutic interchange should incorporate input from the patient, potentially their family, and members of the healthcare team.

4.2. Therapeutic Substitution

In contrast, *therapeutic substitution* is markedly different than therapeutic interchange. This strategy occurs without the prior authorization of the initial prescriber. The use of therapeutic substitution is rare. This strategy should never be accepted unless reviewed and approved by the healthcare team based on the science available.

4.3. Generic Substitution

Generic substitution refers to switching between a branded drug and its therapeutically equivalent generic version. Many pharmacy and medical organizations have addressed this issue, especially as it pertains to generic substitution of narrow therapeutic index and critical dose drugs (50,56–64). As highlighted earlier, generic substitution laws are state specific. In most states, pharmacists cannot substitute nontherapeutic equivalent products. Some states allow substitution between products as long as state-specific criteria are met, such as having the same active ingredient, dosage form, dose, and route of administration.

5. Issues

5.1. Level of Evidence

The concept of *level of evidence* plays a central role in evaluation of data and guideline development. For ACCF/AHA, the following graded scheme is widely used: Level of Evidence: A, data derived from multiple randomized clinical trials; Level of Evidence: B, data derived from a single randomized trial or nonrandomized studies; and Level of Evidence: C, consensus of experts.

Level of evidence has great implications for the field of therapeutic interchange. Terms such as *equivalence, superiority, noninferiority, pragmatic clinical trials,* and *comparative effectiveness* require careful evaluation. Studies that use those statistical terms to evaluate endpoints must be critically reviewed.

A particularly important concept relates to interpretation and inference in noninferiority randomized controlled trials. In comparing drugs or devices in this setting, either a superiority or a noninferiority design is chosen. In the former, the objective is to test a new drug versus either another drug or a placebo with the aim of demonstrating that the new drug is statistically significantly better than the comparator. Important considerations include the "power" to detect the difference between the new drug and the comparator. The finding of superiority in such a trial is of great importance.

The other approach is a noninferiority design. This trial design may either compare a new drug with an older one or one of a different class or, less frequently, a placebo. It is intended to demonstrate that the drug of interest is not worse than the drug with which it is compared. Interpretation of noninferiority trials is complicated because they rest on identifying a pre-specified margin within the boundaries of which it can be concluded that the drug is not worse than its comparator. It is important to remember that documenting noninferiority is not the same as documenting equivalence. The boundaries of this margin are critical; in some studies, these margins are based on prior studies; in others, an absolute margin is chosen. For example, the new drug might be deemed noninferior if the outcome of interest is shown to be no >2% worse (with 95% confidence) versus the comparator. In other trials, the margin is based on preserving a certain amount of the previously established benefit (e.g., at least 50% of the benefit) of the comparator with the new drug. FDA guidelines emphasize that noninferiority should be identified using both clinical and statistical margins.

Randomized clinical trials of drug research were evaluated by Wangge et al. (65) in 227 articles that reported 232 noninferiority trials. These authors reported that although 97.8% of the trials reported the noninferiority margins, only 45.7% described how the margin was defined. Although FDA guidelines exist for the determination of margins, <10% of the trials documented that the noninferiority margin was based on appropriate clinical margins. Even more troublesome was the finding by these authors that >8% of the trials were interpreted incorrectly.

These issues related to trial design and performances are extremely relevant to the field of therapeutic interchange. This relates to the fact that substitution of 1 drug or a class of drugs is often based on the assumption that 1 is noninferior.

5.2. Outpatients and Medication Reconciliation

Therapeutic interchange and generic substitution programs have been used in the hospital setting for many years because a single formulary simplifies prescribing decisions as well as the inventory control process (48). The outpatient or ambulatory care setting is not as straightforward and presents its own set of challenges. Care must be taken when patients transition to and from inpatient and outpatient settings. During hospitalization, documentation of medication changes, their rationale, and whether changes are temporary or permanent is often lacking. As a result, an estimated 19% to 23% of patients suffer an adverse drug event after discharge (66).

The American Medical Association strongly recommends that therapeutic interchange in patients with chronic diseases who are stabilized on a drug therapy regimen be discouraged (51). However, if a therapeutic interchange is made during hospitalization, care must be taken to ensure that the patient is switched back to the home medication at discharge. If not, therapeutic duplication is possible if the patient then resumes taking their home medication as well, which can lead to toxicity and possible adverse effects. In addition, if a new therapy is initiated in the hospital setting, there is no guarantee that the same medication will be continued after discharge. Outpatient drug programs constantly change their formulary, and patients may change insurance providers and thus be exposed to different formularies (48). Effective transfer of information from the hospitalist to outpatient provider at discharge should include timely, accurate, and complete documentation of discharge medications.

5.3. Validation in Quality of Substituted Drug

One of the most persuasive arguments for generic substitution is cost containment, a critical component of health care. The 1984 Hatch-Waxman Act authorized the FDA to approve generic drugs that were demonstrated by the manufacturer to be bioequivalent (2). The initial test-to-reference ratio was 75% to 125% but was subsequently modified to 80% to 125%. The components of this metric vary on dose administered, gut wall absorption, site of activity, therapeutic effect, the width of the narrow therapeutic window, and the ratio of treatment effect to drug side effects. The definition of *biologically equivalent* is therefore of crucial importance and can vary based on inert binders, manufacturer curves, area under the curve, as well as the function of time. All of these could have important implications.

A particularly important issue is that of the prespecified equivalence of boundaries between the 2 drugs—brand name versus generic. For this comparison, it must be remembered that some variability can exist within the reference product itself. Typically, a prespecified equivalence of 80% to 125% might be satisfactory to meet the criteria of equivalence if the risk–benefit ratio is wide. For drugs with a more narrow risk–benefit ratio, that wide confidence interval would have important implications for risk or benefit.

Although much of the literature is related to medications used for seizure control where small differences of drug availability or activity may have profound influence on patient outcome, there is also abundant albeit somewhat contradictory information in the cardiovascular literature.

An important example of drug selection involves warfarin. Only a few, small prospective randomized controlled trials including clinical endpoints compared generic and brand-name warfarin. Whereas some suggest alterations in INR occur after a switch in medications (67), other reports indicate no consistent impact on INR after switching from brand name to generic warfarin (68,69). One large-scale study of older individuals in Canada demonstrated conversion of 87% of prescriptions to generic medication with no changes in rates of INR testing, hospitalization for major hemorrhage, or cerebral thromboembolism (70). Careful review of the available evidence thus supports the decision for generic substitution of warfarin with appropriate clinical oversight and monitoring.

5.4. Class Effect

Drug substitution within the same class of drugs further increases the complexity of therapeutic interchange. Whereas with generic substitution therapy, clinical tests should not be needed when a generic drug is substituted for a brand name, based upon statistical and clinical analysis that indicates no difference >20% between the generic and brand-name drug in terms of safety and efficacy. As mentioned before, in drugs with a low or marginal risk–benefit ratio, this may make a significant difference. This adherence, however, is magnified when there is a substitution of drugs in the same class. This may have very important implications.

In this setting, although the 2 drugs may have similar properties, the end result may be very different. A common scenario would be substitution of the generic statin, simvastatin, for atorvastatin (Lipitor). Both are categorized for use for hyperlipidemia, but both may have additional and different pleotrophic actions that may affect more than just the property of reducing LDL cholesterol. In addition, the side effect of myalgias may also be very different as is the per-milligram strength of atorvastatin (Lipitor) versus simvastatin. Generic substitution by covered health plans is very often the result of economic decisions and is heavily driven by cost. These switches do not put the patient and treating physician at the center of the decision-making pathway. Such simple mandated switches from a covered health plan from atorvastatin (Lipitor) to simvastatin could have major unintended consequences. Physicians and healthcare personnel should be cognizant of potential unintended consequences. The patients should also be notified of potential unintended consequences. If recognized, the physician and healthcare team should have the opportunity to resolve these issues in concert with the covered health plan.

Another commonly used class of drugs in patients with cardiovascular disease are the phosphodiesterase inhibitors used for erectile dysfunction. All of these drugs are given with caution in patients with cardiovascular disease, especially when vasodilators are given concomitantly. However, 1 of the drugs, vardenafil (Levitra) prolongs QT interval similar to moxifloxacin (Avelox) (71), whereas sildenafil (Viagra) and tadalafil (Cialis) do not have such a warning in their label. In some patients, these phosphodiesterase inhibitors might be considered interchangeable. In cardiac patients, especially those with risk for QT prolongation or drug-induced torsades de pointes, interchange may not be advisable.

5.5. Restriction of Drug Availability

This issue has become increasingly complex, involving several factors including legal, regulatory, equivalence, and economics. Some of these issues relate to drugs or devices that can be purchased outside the United States but are not yet approved in the United States. Some of them are drugs that are still on patent in the United States but can be manufactured as generic drugs and purchased in other countries (e.g., Canada), and some relate to the identical drugs that are sold at a "discount" in other countries. This is further complicated by restrictions of institutional formulary listings, insurance coverage, and sale of drugs online because they are not available in the United States. One relevant example is clopidogrel (Plavix), which is manufactured by sanofi-aventis. This drug has a Class I indication for patients who receive a drug-eluting stent for treatment of coronary artery disease. The duration of administration varies from several months to indefinitely when used to prevent stent thrombosis. This specific drug is covered by U.S. patent protection until May 2012. Until recently, there was no acceptable substitution. The cost of this drug varies substantially, such that the cost for patients in some areas of the United States can be as much as $6 per day, which may not be economically feasible for many patients. A Canadian company manufactures a generic drug that was priced approximately 30% lower than Plavix (72) and was sold in Canada and some pharmacies in New England. Pharmacokinetics reported that this drug met the testing requirements for a generic drug. However, despite this generic documentation, the drug was barred from sale in the United States. Other relevant examples include drugs such as dabigatran and ticagrelor, both of which had advantages as antithrombotic agents available in Europe before FDA approval in the United States. It is important to highlight that the Federal Food, Drug, and Cosmetic Act prohibits persons from importing into the United States any prescription medication that has not been approved by the FDA for sale (73). However, the FDA has developed specific guidelines for coverage of personal importations with respect to the personal use of unapproved drugs (74).

The FDA may allow for an individual entering into the United States to import no more than a 3-month supply of an unapproved drug if all the following conditions are met: the intended use of the drug is for a serious condition in which effective treatment is not found domestically; the

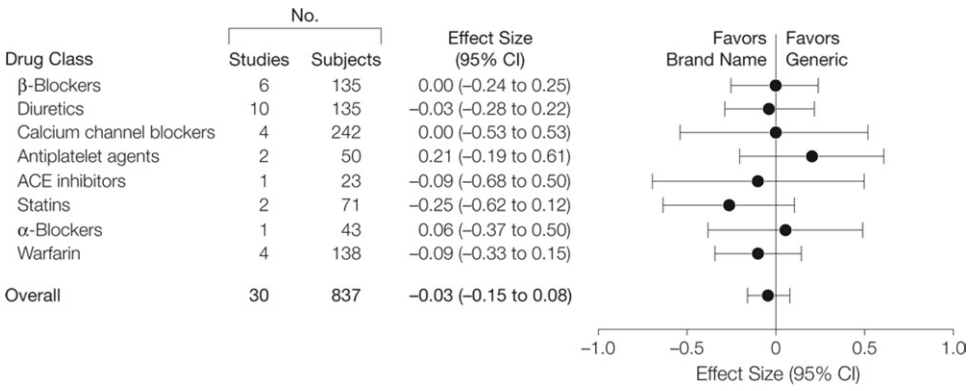

Figure 2. Results of Meta-Analyses of Trials Comparing Classes of Generic and Brand Name Drugs Used for Cardiovascular Conditions

ACE indicates angiotensin-converting enzyme; and CI, confidence interval. Reprinted with permission from Kesselheim et al. (77). Copyright 2008 American Medical Association.

drug will not be distributed commercially; the drug does not present an unreasonable risk; and the individual has in writing a statement that the drug is for his or her own personal use and provides the name and address of the licensed physician in the United States responsible for his or her treatment with the drug (74). Export of larger quantities is illegal. The issue of new as well as generic drugs not available in the United States but available in the rest of the world is apt to increase as worldwide manufacturing facilities become more widely available.

6. Specific Populations

There are other very important groups of patients in which therapeutic interchange/substitution may have markedly adverse consequences. In these groups, the risk–benefit ratio of every therapeutic interchange/substitution needs to be carefully reviewed, taking into consideration the specific drug and the specific patient or clinical setting on a case-by-case basis.

6.1. Elderly Patients

Elderly patients in the United States (defined as ≥65 years of age) are the most likely to have chronic medical and especially cardiovascular conditions that require treatment. More than 80% of elderly patients take at least 1 medication every day and, as a group, consume one third of all prescribed drugs (75). The physiological effects of aging on pharmacokinetics affect the absorption, distribution, metabolism, and elimination of drugs, but these changes have considerable individual variability and are hard to predict. Nonetheless, characteristics of older patients that predispose them to adverse drug effects or sensitize them to drug effects include a greater severity of illness, multiple comorbidities, smaller body size (especially for women), and lower rates of hepatic and renal metabolism and excretion (75).

Little information is available specifically about substituting medications in the elderly. Even for clinical trials designed specifically to examine older adults, limited enrollment of selectively higher functioning subjects makes subsequent generalizations about study findings problematic. For example, in SHEP (Systolic Hypertension in the Elderly Program), only 1% of screened persons were enrolled, and 95% of those were living independently (76). Thus, most information about drug substitutions is derived from studies that did not enroll large numbers of older patients. In a comprehensive meta-analysis of studies comparing treatment with cardiovascular brand-name drugs with generic drugs, essentially no differences in effect size were seen for beta blockers, diuretics, calcium channel blockers, antiplatelet agents, ACE inhibitors, statins, alpha blockers, or warfarin (Figure 2) (77). Although the findings provide some reassurance about the relative equivalence of generic medications, the number of subjects in each study was small, and the extrapolation to older individuals cannot be made with certainty.

Caution and monitoring are indicated in prescribing medications to older patients. Risks of adverse consequences could be minimized by avoiding strict adherence to prescribing guidelines; knowing the pharmacology of the drugs prescribed; limiting the number of drugs prescribed; determining the dosage based on an individual patient's overall condition and comorbidities—generally starting at lower doses; and importantly, surveying effectiveness and untoward effects, particularly after the transition from an in-hospital to outpatient setting (75).

6.2. Pediatric Patients

The Committee on Drugs of the American Academy of Pediatrics published their initial Policy Statement on Generic Prescribing, Generic Substitution, and Therapeutic Substitution in 1987 (78) and reaffirmed it in 2009 (79). Based on the lack of evidence supporting the assumption of bioequivalence for most therapeutic agents in infants and children, the Committee did not support a blanket recommendation for generic substitution. They also strongly opposed any attempt to allow the practice of therapeutic substitution. Therapeutic interchange was not specifically addressed.

This conservative position is largely based on the fact that much of what we know regarding the pharmacokinetics, pharmacogenomics, efficacy, and safety of many drugs in children is extrapolated from the adult experience. Applying

data derived from studies conducted in adults or experimental systems of adult origins may have limited applicability to pediatric disease. This has been highlighted in a review examining tacrolimus pharmacokinetic and pharmacogenomic differences between adult and pediatric transplant recipients (80). Inherent physiological differences exist in the young child, including less effective plasma binding proteins, altered expression of intestinal P-glycoprotein, and increased expression of phase 1 metabolizing enzymes, resulting in clinically significant differences when administering tacrolimus to a child (80).

Recent data demonstrate that only 25% of approved drugs marketed in the United States have adequate pediatric data to support approval of product labeling by FDA for dosing, safety, or efficacy in children (81). It was not until 1994 that a series of legislative changes targeted improved drug therapy in children of all ages. In that year, the FDA Pediatric Rule provided an avenue for manufacturers to insert information pertaining to the clinical pharmacology and therapeutic use of drugs in pediatric patients into approved product labeling (82). The FDA Modernization Act of 1997 then provided an incentive for the pharmaceutical industry to complete pediatric studies of marketed drug products. This Pediatric Exclusivity Provision provided an additional 6 months of patent protection, or marketing exclusivity, in return for performing studies specified by the FDA (81). The Best Pharmaceuticals for Children Act of 2002 and the Food and Drug Amendments Act of 2007 extended the economic incentives provided by pediatric exclusivity. In the 10 years since the start of the program in 1997, >115 products had a labeling change. Approximately one third of these labeling changes showed an important difference in the pediatric dosing, safety, or efficacy compared with adult patients that will likely result in long-term health benefits for children (81). In September 2010, the National Institute of Child Health and Development awarded a contract to establish a Pediatric Trials Network to provide an environment and an appropriate infrastructure for conducting safe and effective pediatric clinical trials for the Best Pharmaceuticals for Children Act.

Despite the relative paucity of data, the practices of generic substitution and therapeutic interchange are recognized and accepted in many pediatric healthcare settings. Based on pharmacological equivalence, clinical evidence, cost, medical staff involvement, and opportunity for variance, institutional drug–setting bodies such as pharmacy and therapeutic committees identify therapeutic classes amenable to interchange, and update based on the evolving literature. Contrary to adults, the number of drug classes and agents chosen for therapeutic interchange in pediatric patients is much more limited. Common cardiovascular classes of drugs selected for interchange in adult patients may include statins, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and beta-adrenergic blocking agents (43). In contrast, only statins may be permitted to be interchanged within class in pediatric patients (83).

6.3. Female Patients

Selecting cardiovascular medications for women requires additional and sometimes different considerations compared with prescribing for men. Pharmacodynamic differences exist for women related to lower weight, lower volume of distribution, and lower renal drug clearance in women (84). In addition, sex-based prolongation of the QT interval warrants caution in the prescription of cardiovascular and noncardiovascular drugs that may potentially prolong the QT interval and lead to serious arrhythmias. Other cardiovascular drug-related adverse effects more common in women include hemorrhagic complications of anticoagulants and antiplatelet drugs, electrolyte abnormalities with diuretics, myopathy with statins, and cough with ACE inhibitors (84). A specific example relates to the use of digoxin. In a post hoc analysis of the Digitalis Investigation Group (DIG) trial, there was a suggestion that digoxin use was associated with an increased risk of mortality in women with heart failure and a left ventricular ejection fraction ≤45% compared with men (85). These poor outcomes have been related to the fact that these women exhibited higher digoxin serum concentrations, possibly because of the drug–drug interaction between hormone replacement and digoxin (86). In addition, because serum creatinine was used to calculate the digoxin dose, serum creatinine may not be a good marker of chronic kidney disease in women (87).

Initial therapeutic decisions are also complicated by the fact that the evidence base for medication effectiveness in women is limited. Most randomized clinical trials (with few notable exceptions) (88) have enrolled a minority of women, thus limiting generalizability of the findings to women. It is also worth mentioning that many manufacturers purposefully avoid the study of women of childbearing age to limit their legal liability, not because of scientific issues as the primary concern. When studied specifically in women, sex differences in outcomes are apparent. For example, the use of aspirin was not effective in lowering cardiovascular outcomes in women <65 years of age who were not at high risk for stroke in the Women's Health Study (89). Whether this is a differential effect of ASA on outcome by sex among primary prevention patients or whether the effect was related to baseline risk is unclear. Thus, general principles of individualized drug and dose selection, careful monitoring of intended effect and side effects with initial drug and especially after drug substitution, and minimizing total number of medications should be adhered to for women.

Pregnancy also requires heightened considerations about drug selection for both the mother and fetus. A number of alterations occur during pregnancy that may influence the availability, elimination, action, and side effect profile of medications. Absorption and bioavailability of drugs may vary with intestinal motility and acid secretion during stages of pregnancy. Hemodynamic changes with gestation affect

the volume of drug distribution and may impact renal elimination because of increased cardiac output. Treatment of any condition with drugs that were at steady state prior to pregnancy will require reassessment for efficacy and adverse effects throughout pregnancy. In addition, the interface of the placenta and fetus impacts drug transmission to the fetus and must always be considered in deciding the choice and dose of a drug to be used for maternal conditions during pregnancy (90). Other considerations include the fact that drug selection for women of child-bearing age must account for the possibility of unplanned pregnancies and early, undetected pregnancy that could unknowingly expose the developing fetus to pharmaceutical agents (91).

6.4. Immunocompromised Patients

Immunocompromised patients, including those who have received organ transplants, are at high risk of drug interactions because of the multiple drugs required for chronic administration to prevent rejection, treat the underlying condition, treat or prevent infection, and treat or prevent many comorbid conditions. Knowledge of all agents, specifically regarding their pharmacokinetics and therapeutic equivalency, is required to minimize adverse drug reactions and drug–drug interactions (92). For example, cyclosporine is marketed as oil-base (Sandimmune) and modified, microemulsion (Gengraf and Neoral) formulations. Although Gengraf and Neoral are therapeutically equivalent and can be interchanged, neither product can be interchanged with Sandimmune (1). Potential interchange of Sandimmune for either Gengraf and Neoral could result in significantly erratic cyclosporine blood concentrations (58). Concern also exists when generic-to-generic switches occur with immunosuppressants. As of 2011, 4 generic oral tacrolimus and 11 oral mycophenolate mofetil products are on the market with bioequivalency ratings of AB (1). The effect of such switches between generics on serum drug concentrations and patient outcomes remains unknown.

6.5. Acute Coronary Syndrome Patients

Acute coronary syndromes (ACS) are frequent, and patients with these conditions are often treated with multiple medications, raising the potential not only for drug-drug interactions, but also the potential for multiple therapeutic interchange/substitution episodes. Commonly used drugs in this setting include glycoprotein IIb/IIIa inhibitors and LMWHs.

6.5.1. Glycoprotein IIb/IIIa

In the former group, there are several drugs including the antibody fragment abciximab, and the small molecules tirofiban and eptifibatide all inhibit the platelet glycoprotein IIb/IIIa receptor (93,94). Some hospitals may only have 1 or 2 available for clinical use on the formulary. The drugs, however, are very different, based on their structure, metabolism, and effect on outcomes in patients treated with percutaneous coronary intervention or for acute coronary syndromes (93). Eptifibatide, for example, has been susceptible to overdosing in patients with reduced renal function (95). There is a specific, well-known relationship between creatinine clearance and these drugs. This relationship affects selection and dosing to be ordered. Healthcare providers in individual practices should be aware of these differences and base treatment strategies on the availability of specific drugs, altering strategies as appropriate.

6.5.2. Anticoagulants

Anticoagulants are also used ubiquitously. These include LMWH, unfractionated heparin, bivalirudin (Angiomax), and fondaparinux (Arixtra). The specific use of each of these depends upon multiple factors, including patient factors, timing of administration, and specific drugs available. They are not interchangeable. For example, bivalirudin has been approved for percutaneous coronary intervention procedures but not as a part of routine medical care of unstable angina. Although fondaparinux can be used during percutaneous coronary intervention, it must be combined initially with another anticoagulant with at least factor IIa activity. Such a therapeutic strategy avoids thrombus formation in the catheters (96). A number of LMWHs are available; these have often been subject to therapeutic substitution based largely on economic considerations (97). Although there have been a large number of clinical trials to define which agents (and doses) have the strongest evidence for various clinical conditions, healthcare providers have been pressured by many hospitals to use a single agent to qualify for reduced purchasing costs. As previously mentioned, specific LMWHs, as well as generic LMWH, may exhibit assay-based differences and immunogenicity profiles. Accordingly, healthcare teams need to be vigilant about therapeutic interchange in this patient group.

6.5.3. Antiplatelet Agents

Antiplatelet agents are an essential component of care in this setting. Clopidogrel (Plavix) has been a cornerstone. As previously mentioned, there is an abundant amount of data on the pharmacogenomics and pharmacodynamics of clopidogrel administration (13). This has the potential to affect safety and outcome, although complete resolution of this question has not been reached. Options in selected centers include the substitution of newer drugs; for example, prasugrel, although the risk–benefit ratio of these newer agents may be different from clopidogrel because of the marked increase in bleeding if administered to patients with a very small body weight, those >75 years of age, or patients with prior stroke. Such considerations must be taken into account if therapeutic interchange is considered in this setting.

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6.5.4. Fibrinolytic Agents

Fibrinolytic agents have been used for reperfusion therapy of ACS patients with ST-segment elevation myocardial infarction and are still indicated in patients who do not have prompt access to catheterization laboratories. Fortunately, large-scale head-to-head comparison studies have evaluated the relative strengths of these agents that differ widely in chemical structure, antigenicity, and administration. Some of these head-to-head trials have documented clinical superiority of a specific fibrinolytic agent. For example, tissue-type plasminogen activator has been shown to be superior to streptokinase. However, in many hospital settings, only a limited number of these agents are available. This has important implications. Only tissue-type plasminogen activator is approved for use in acute ischemic stroke. The safety and efficacy of other fibrinolytic agents for the treatment of acute ischemic stroke have not been demonstrated, and experimental protocols that have translated the standard dosing for acute myocardial infarction to the treatment of acute ischemic stroke have resulted in excessive rates of intracranial hemorrhage. Accordingly, in some institutions, tissue-type plasminogen activator may be the only option available.

6.5.5. Proton Pump Inhibitors

Proton pump inhibitors are widely used in this setting to minimize the potential for gastrointestinal bleeding. They have been the object of therapeutic substitution to enable purchasing agreements or switch to less expensive alternatives, by hospitals and in outpatient settings (98), with mixed success. Given observations regarding differential effects on drug metabolism enzymes, such as CYP2C19, it is possible that such substitutions could have unintended consequences (13). There has been concern that rates of subsequent stent thrombosis may be affected in patients treated with clopidogrel who also are given a proton pump inhibitor. These potential effects of coadministration of $\geq$1 specific proton pump inhibitors and clopidogrel on subsequent stent thrombosis are of great importance. This has implications for the use of alternative antiplatelet strategies as well as alternative strategies to minimize gastrointestinal bleeding based upon the risk profile of the specific patient (13).

These examples of clinical settings in patient populations are representative of the crucial importance of patient characteristics, clinical presentation, comorbid conditions, and specific drug regimens selected that must be considered in selecting specific therapeutic strategies. They emphasize the critical nature of the team care approach to patients, with involvement of cardiologists, nursing staff, and pharmacologists to match the correct drug and correct dose with the correct patient and clinical situation to optimize outcome. Such a team approach has been emphasized by the Institute of Medicine to minimize medical errors and optimize outcome.

7. Recommendations

1. Therapeutic substitution and therapeutic interchange refer to 2 distinctly different practices. Therapeutic substitution should not be accepted. When considering therapeutic interchange, third-party payers must take into account multiple factors when approving the interchange such as level and strength of evidence for the medication and the patient's specific medical condition. Cost should be a consideration in this decision but not be the primary factor.
2. Each healthcare facility should have a formally chartered interdisciplinary pharmacy and therapeutics committee charged with ensuring medication safety and developing an evidence-based formulary. The committee's charge should include the development of policy for therapeutic interchange/substitution. Decisions and recommendations should be reviewed at least annually to address new evidence as it becomes available.
3. All formulary decisions should be made based primarily on the recommendations of the healthcare team after considering the scientific evidence in the specific patient or patient groups to be treated and the ratio of risk/balance in that setting. These decisions should be widely and proactively promulgated to prescribing physicians and include provisions for appeals both at the policy level and for individual patient exceptions. Economic considerations, although of substantial importance, should only be addressed after those other considerations have been fully evaluated.
4. All payers that consider instituting a therapeutic interchange policy should ensure that all healthcare teams have the information necessary, as outlined in this document, to provide guidance to prescribing physicians. Such guidance should be proactively given so that it is available at the point of care.
5. After initiating a therapeutic interchange policy, healthcare systems are responsible for implementing processes for informing individual patients of the change in medications prescribed.
6. Applicable state, federal, and international policies concerning metrics of equivalence, manufacturing, packaging, and purity need to be monitored annually, at minimum. These policies should be followed by the pharmacy and therapeutics committee with the appearance of new formulations or generics on the market and when issues surrounding product manufacturing, packaging, and purity are reported by specific manufacturers or the FDA. It is very important for healthcare teams to have full and timely access to measures of bioequivalence in generic drugs.
7. Pharmacists must understand both the rationale for and use of the *Orange Book*. Contemporary pharmacy practice requires confirmation that a substituted generic drug is bioequivalent to the prescribed product. At the state level, policymakers overseeing generic

substitution should encourage consistency in regulations and recommend pharmacists use the *Orange Book* in determining whether bioequivalence has been documented between the generic medication and the prescribed product. When dispensing medications for chronic conditions, a pharmacist should communicate to the patient both verbally and in writing (e.g., on the label of the prescription bottle) when a medication's manufacturer has changed. This is of particular importance when dispensing a narrow therapeutic index/critical dose medication.

8. Pharmacogenomics may have a substantial impact on the field in the future. As scientific data and evidence continue to emerge and technologies improve, policies should be adapted as needed. This may enhance the ability to personalize medical care for the individual patient.
9. Special groups of patients with unique requirements, such as immunocompromised patients, pediatric patients, women—particularly those who are pregnant—or the elderly who require multiple medications in the setting of acute or chronic illness, should be given special consideration before therapeutic interchange is implemented. This is of significant importance when drugs that have a narrow therapeutic/toxicity ratio are being administered or considered.

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Key Words: ACCF health policy statement ■ drugs, generic ■ formularies ■ therapeutic equivalency.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—ACCF/AHA 2011 HEALTH POLICY STATEMENT ON THERAPEUTIC INTERCHANGE AND SUBSTITUTION

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David R. Holmes, Jr *(Chair)*	Mayo Clinic—Consultant, Cardiovascular Diseases	None	None	None	None	None	None
Jeffrey A. Becker	Children's National Medical Center—Director, Outpatient Cardiology	None	None	None	None	None	None
Christopher B. Granger (Recused from voting on recommendations)	Duke Clinical Research Institute—Associate Professor of Medicine; Director, Cardiac Care Unit	• AstraZeneca • Boehringer Ingelheim* • Bristol-Myers Squibb • GlaxoSmithKline • Hoffman La Roche • Novartis • Otsuka • Sanofi-aventis* • The Medicines Company	None	None	• Astellas* • AstraZeneca* • Boehringer Ingelheim* • Bristol-Myers Squibb* • GlaxoSmithKline* • Medtronic Vascular • Merck* • Sanofi-aventis* • The Medicines Company*	None	None

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Marian C. Limacher	University of Florida, Division of Cardiovascular Medicine—Senior Associate Dean for Faculty Affairs and Professional Development; Suncoast Endowed Professor of Cardiovascular Research	None	None	None	None	None	None
Robert Lee Page II	University of Colorado School of Pharmacy—Associate Professor of Clinical Pharmacy	None	None	None	None	None	None
Cathy Sila (Recused from voting on recommendations)	Case Western Reserve University School of Medicine, Neurological Institute Case Medical Center—George M. Humphrey II Professor of Neurology; Director, Stroke & Cerebrovascular Center	• Axio • Elekta • EvaHeart Medical† • Hoffman La Roche • Monteris	None	None	• AGA Medical†	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity; or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*Significant relationship. †No financial benefit.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—ACCF/AHA 2011 HEALTH POLICY STATEMENT ON THERAPEUTIC INTERCHANGE AND SUBSTITUTION

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Biykem Bozkurt	Official Reviewer—AHA	None	None	None	• Forest Pharmaceuticals*	• Amgen • Corthera • Novartis	None
Robert A. Harrington	Official Reviewer—ACCF Clinical Quality Committee	• APT Nidus Center • AstraZeneca* • Baxter • Bristol-Myers Squibb • CSL Behring • Eisai • Gilead Sciences • Merck • Mitsubishi-Tanabe • Novartis† • Orexigen Therapeutics • Regado • Sanofi-aventis • Schering-Plough*	None	None	• AstraZeneca • Baxter • Bristol-Myers Squibb* • GlaxoSmithKline* • Merck* • Portola* • Schering-Plough* • The Medicines Company	None	None
Roger Kelley	Official Reviewer—AHA	None	None	None	None	None	None

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Richard J. Kovacs	Official Reviewer—ACCF Board of Trustees	• Biomedical Systems • Cook Incorporated-Medical Institute* • Eli Lilly* • Essentialis • Xenoport	None	None	None	None	None
Thomas J. Lewandowski	Official Reviewer—ACCF Board of Governors	None	• AstraZeneca	None	None	None	None
Jafna L. Cox	Content Reviewer—ACCF Board of Governors	• AstraZeneca • Bayer • Boehringer Ingelheim • Sanofi-aventis	None	None	• Pfizer*	None	None
Joseph P. Drozda, Jr.	Content Reviewer—Clinical Quality Committee	None	None	None	None	None	None
Harlan M. Krumholz	Content Reviewer—Clinical Quality Committee	• Centegen/Life Technologies*	None	None	None	None	None
G.B. John Mancini	Content Reviewer—ACCF Board of Governors	• GlaxoSmithKline • Merck • Pfizer • Sanofi-aventis	None	None	• Merck*	None	None
Frederick A. Masoudi	Content Reviewer—Clinical Quality Committee	None	None	None	None	None	None
John F. Robb	Content Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Robert N. Vincent	Content Reviewer—Adult Congenital/Pediatric Cardiology Council	None	None	None	None	None	None
Lawrence Yu	Content Reviewer—U.S. Food and Drug Administration	None	None	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity; or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

*Significant relationship. †No financial benefit.

ACCF indicates American College of Cardiology Foundation; and AHA, American Heart Association.

APPENDIX 3. STATE LAWS OR STATUTES GOVERNING GENERIC SUBSTITUTION BY PHARMACISTS

State	Allows for Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Mandates Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Allows for Brand If Requested by Patient	Mandates Brand Only If Indicated by Physician	To Ensure Brand Name Only, Physician Must Indicate the Following on the Written Prescription OR Communicate Orally
Alabama	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written."
Alaska	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Arizona	√		√	√	Clearly display on the prescription "DAW" or other wording indicative of Substitution Not Permitted.
Arkansas	√		√	√	In the physician's handwriting, indicate that the product ordered should not be substituted.
California	√		√	√	In the physician's handwriting, the words "Do Not substitute" must appear on the prescription.
Colorado	√		√	√	In the physician's handwriting, the words "Dispense As Written" must appear on the prescription.
Connecticut	√		√	√	In the physician's handwriting, indicate that the product ordered should not be substituted.

State	Allows for Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Mandates Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Allows for Brand If Requested by Patient	Mandates Brand Only If Indicated by Physician	To Ensure Brand Name Only, Physician Must Indicate the Following on the Written Prescription OR Communicate Orally
Delaware	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written."
Florida		√	√	√	In the physician's handwriting, the words "Medically Necessary" must appear on the prescription.
Georgia	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Hawaii		√	√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription. **Mandates Brand Only for Anticonvulsant Medications.**
Idaho	√		√	√	Physician must indicate "Brand Only" by checking the "Brand Only" box on the prescription.
Illinois	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense AS Written."
Indiana	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written."
Iowa	√		√	√	Physician shall communicate to pharmacist that product should not be substituted.
Kansas	√		√	√	In the physician's handwriting, the words "Dispense As Written" must appear on the prescription.
Kentucky		√	√	√	In the physician's handwriting, the words "Do not substitute" must appear on the prescription.
Louisiana	√		√	√	Physician must indicate "Brand Only" by checking the "Dispense as Written or DAW" box on the prescription.
Maine		√		√	In the physician's handwriting, the words "Dispense As Written," "DAW," "Brand," or "Brand Necessary" must appear on the prescription.
Maryland	√		√	√	Physician shall communicate to pharmacist that product should not be substituted.
Massachusetts		√		√	In the physician's handwriting, the words "No Substitution" must appear on the prescription.
Michigan	√		√	√	In the physician's handwriting, the words "Dispense As Written" or "DAW" must appear on the prescription.
Minnesota		√	√	√	In the physician's handwriting, the words "Dispense As Written" or "DAW" must appear on the prescription.
Mississippi	√		√	√	Physician shall communicate to pharmacist that product should not be substituted.
Missouri	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written."
Montana	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Nebraska	√		√	√	In the physician's handwriting, the words "Dispense As Written," "DAW" or similar statements must appear on the prescription.
Nevada		√	√	√	In the physician's handwriting, the words "Dispense As Written" must appear on the prescription.
New Hampshire	√		√	√	Physician must specify that the Brand is Medically Necessary.
New Jersey		√	√	√	Physician must initial next to the option "Do Not Substitute" on the prescription.
New Mexico	√		√	√	In the physician's handwriting, the words "No Substitution" or "No Sub" must appear on the prescription.

State	Allows for Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Mandates Generic Substitution by Pharmacists If "Brand Only" Not Indicated by Physician	Allows for Brand If Requested by Patient	Mandates Brand Only If Indicated by Physician	To Ensure Brand Name Only, Physician Must Indicate the Following on the Written Prescription OR Communicate Orally
New York		√		√	In the physician's handwriting, "DAW" must appear on the prescription.
North Carolina	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written." **Narrow Therapeutic Range Drugs must be dispensed as originally prescribed.**
North Dakota	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Ohio	√		√	√	In the physician's handwriting, the words "Dispense As Written" or "DAW" must appear on the prescription.
Oklahoma	√		√	√	Physician shall communicate to pharmacist that product should not be substituted.
Oregon	√		√	√	In the physician's handwriting, the words "No Substitution" or "N.S" must appear on the prescription.
Pennsylvania	√		√	√	Physician shall communicate to pharmacist that product should not be substituted.
Rhode Island		√	√	√	In the physician's handwriting, the words "Dispense As Brand Name Necessary" must appear on the prescription.
South Carolina	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense as Written."
South Dakota	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Tennessee		√	√	√	In the physician's handwriting, the words "Dispense As Written," "DAW," or other language of intent must appear on the prescription.
Texas	√		√	√	In the physician's handwriting, the words "Brand Necessary" or "Brand Medically Necessary" must appear on the prescription.
Utah	√		√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written" OR in the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Vermont		√	√	√	In the physician's handwriting, the words "Brand Necessary" or "No substitution" must appear on the prescription.
Virginia	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Washington		√	√	√	Sign the prescription signature line labeled "May Not Substitute" or "Dispense As Written."
West Virginia		√	√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Wisconsin	√		√	√	In the physician's handwriting, the words "No Substitutions" or "N.S." must appear on the prescription.
Wyoming	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.

The information presented in this chart is for reference only. Prescribers, please consult the appropriate authorities in your state for specific requirements and wording to be sure that medications are dispensed as you have determined appropriate for your patient. Any questions should be directed to those authorities. Reprinted with permission from Epilepsy Therapy Project (99). This information was reviewed and verified as current in February 2010.