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Internal Medicine

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ABSTRACT & COMMENTARY

Risk of Developing Atrial Fibrillation with Use of Bisphosphonates

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: The risk of developing atrial fibrillation is increased by the use of oral or intravenous bisphosphonates, but the risk is relatively greater when the drug is given intravenously.

SOURCE: Sharma A, et al. Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. *Am J Cardiol* 2014;113:1815-1821.

Bisphosphonates are usually used as the first-line therapy for the treatment of osteoporosis and osteopenia because they effectively reduce the risk of osteoporotic fractures.[1] However, recent studies using both the oral and intravenous forms have reported an increased risk of occurrence of atrial fibrillation.[2-9] Because of uncertainty as to whether the intravenous form of bisphosphonate carried a greater risk, Sharma and colleagues performed a systematic review and meta-analysis of the literature from 1966-2013.[10]

The nine studies (135,347 participants) included in the final analysis revealed a statistically significant increased risk of new-onset atrial fibrillation occurring when administering bisphosphonates either intravenously or orally. Moreover, the data suggested that the risk was significantly greater when the drug was used intravenously although the absolute risk remains low (1.1% and 0.4% for intravenous and oral bisphosphonates, respectively).

■ COMMENTARY

The potential pathophysiological mechanisms underlying the apparent association between bisphosphonate administration and the development of atrial fibrillation are not well understood and remain speculative. Alteration of numerous biochemical factors and an increase in a pro-inflammatory state could all be contributing factors. Although the results clearly suggest an association between new-onset atrial fibrillation

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and bisphosphonate use, causality could not be definitely established because detailed data were lacking on associated cardiovascular risk factors such as dyslipidemia, smoking, alcohol consumption, obesity, and concomitant medication use. Obviously, prospective randomized data will be needed to further evaluate the risk of atrial fibrillation with bisphosphonate therapy and to determine whether the association is a "class" effect or is dependent on the specific drug utilized, route of administration of the drug, age of the patient, and/or the presence or absence of one or more of the multiple cardiovascular risk factors. ■

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ABSTRACT & COMMENTARY

Gloves Are Not Perfect

By Eric C. Walter, MD, MSc

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Dr. Walter reports no financial relationships relevant to this field of study. This article originally appeared in the June 2014 issue of *Critical Care Alert*.

SYNOPSIS: After caring for patients with *Clostridium difficile* infection, nearly 25% of health care workers were found to have hand contamination with *C. difficile* spores.

SOURCE: Landelle C, et al. Contamination of healthcare workers' hands with *Clostridium difficile* spores after caring for patients with *C. difficile* infection. *Infect Control Hosp Epidemiol* 2014;35:10-15.

Clostridium difficile is a prominent pathogen in intensive care units (ICUs) and frequently leads to nosocomial infections. One of the most common modes of transmission of *C. difficile* is via the hands of health care workers (HCWs). In this study, Landelle and colleagues aimed to determine how often HCWs' hands became contaminated with *C. difficile* after caring for patients with *C. difficile* infection (CDI). They also identified risk factors for hand contamination.

In this prospective study, HCWs caring for patients with and without CDI were observed daily over an 8-week period. Patients were located in the ICU and medical and surgical hospital wards. Over the course of the study, HCWs caring for seven patients with CDI and 16 control patients without CDI were observed. Observations included patient contact time, level of risk of patient contact (high risk was defined by the possibility of HCWs' hands to be highly contaminated with fecal material), use of gloves, hand hygiene compliance, etc. All patients with

CDI were placed in contact precautions. For HCWs, these precautions included the use of dedicated equipment, donning a disposable gown with full-length sleeves and gloves prior to entering the room, hand hygiene with an alcohol-based solution before wearing gloves, and hand hygiene with soap and water followed by alcohol-based solution after glove removal. HCWs' hands were sampled for *C. difficile* spores immediately after caring for patients, following glove removal, but before hand washing.

Amazingly, and also disturbing, *C. difficile* spores were found on the hands of nearly one out of every four HCWs who had cared for patients with CDI (16/66, 24%). *C. difficile* spores were not isolated from any HCWs caring for patients without CDI (0/44). Having more patient contacts or more contacts with a patient's environment was associated with a higher risk of hand contamination. The number and length of high-risk contacts as well as lack of glove use were also risk factors for hand contamination. After controlling for multiple risk factors using logistic regression, high-risk contact (odds ratio per 1 contact increment, 2.78; 95% CI, 1.42-5.45; $P = 0.003$) and at least 1 contact without the use of gloves (odds ratio 6.26; 95% CI, 1.27-30.78; $P = 0.02$) were associated with hand contamination.

■ COMMENTARY

In this study, Landelle and colleagues report a distressingly high proportion of HCWs found to have hand contamination with *C. difficile*. Remember this study the next time you go to shake the hand of a colleague caring for a patient with CDI. Even more worrisome, 24% may be a low estimate of the proportion of HCWs with hand contamination. In this study, all HCWs knew they were being observed. Despite knowing this, 7.8% of contacts occurred without the use of gloves. In unobserved settings, the lack of glove use is likely to be higher. Despite only 7.8% of contacts occurring without gloves, 24% of HCWs had contaminated hands. Some contamination can be explained by the lack of glove use but 56% of the HCWs with contaminated hands used gloves for all patient contacts. Gloves are not perfect.

There are some limitations to this study. The number of HCWs observed caring for patients with CDI was adequate but not large (n = 66) and there were only seven patients with CDI during the study. HCWs' hands were not sampled for *C. difficile* spores prior to entering patient rooms, so it is possible that contamination was present prior to caring for patients with CDI. However, no spores were identified on the hands of HCWs caring for patients without CDI. It is presumed that hand contamination with spores is a risk for transmission of *C. difficile* but the degree of risk is not known, and this study does not address this question.

In summary, this study offers strong evidence that HCWs' hands become contaminated with *C. difficile* spores during patient care and that glove use and contact precautions decrease the risk of contamination but are not perfect. The implied importance of washing your hands vigorously with soap and water after glove removal should not need repeating. ■

ABSTRACT & COMMENTARY

Frailty: An Important Determinant of Outcome in Critical Illness

By David J. Pierson, MD, Editor

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Dr. Pierson reports no financial relationships relevant to this field of study. This article originally appeared in the June 2014 issue of *Critical Care Alert*.

SYNOPSIS: In this prospective study of older ICU patients (mean age, 67 years), frailty as assessed by a simple scale was present in one-third and was strongly associated with increased risk of adverse events, morbidity, and mortality.

SOURCE: Bagshaw SM, et al. Association between frailty and short- and long-term outcomes among critically ill patients: A multicentre prospective cohort study. *CMAJ* 2014;186:E95-102.

Frailty is an age-associated loss of reserve across multiple physiologic and cognitive systems that leads to increased susceptibility to adverse events. This prospective cohort study carried out in six hospitals in Alberta evaluated all patients aged ≥ 50 years who were admitted to an ICU during an 18-month period for the presence of frailty using a simple, validated scale. The purpose was to determine

Table. Clinical Frailty Scale*		
Frailty Score	Category	Description
1	Very fit	Robust, active, energetic, motivated; commonly exercise regularly; among the fittest individuals for their age
2	Well	No active disease symptoms but less fit than in category 1; exercise or are very active only occasionally (e.g., seasonally)
3	Managing well	Medical problems well controlled, but not regularly active beyond routine walking
4	Vulnerable	Not dependent on others for daily help but symptoms often limit activities; frequently "slowed up" or tired during the day
5	Mildly frail	More evident slowing, needing help in high-order activities of daily living such as finances, transportation, heavy housework, and medications; somewhat impaired with respect to shopping, walking outside alone, meal preparation, and housework
6	Moderately frail	Need help with all outside activities and with housekeeping; often have trouble with stairs and need help with bathing; might need minimal assistance (cuing, standby) with dressing
7	Severely frail	Completely dependent for personal care, from whatever cause (physical or cognitive), but seem stable and not at high risk of dying (for example, within 6 months)
8	Very severely frail	Completely dependent, approaching the end of life; recovery from even a relatively minor illness unlikely
9	Terminally ill	Approaching the end of life; category also applies to persons with life expectancy < 6 months but not otherwise evidently frail
*from Rockwood K, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489-495.		

the prevalence, correlates, and outcomes associated with frailty in this population. With informed consent, patients were enrolled if they were expected to remain in the ICU for at least 24 hours and had not previously participated in the study. Patients were considered to be frail if they had a score > 4 on the Clinical Frailty Scale[1] (*see Table*), as of just prior to hospitalization.

Of 1359 potentially eligible patients during the study period, 421 were enrolled, all of whom were assessed during the hospitalization and at 6 and 12 months. Their mean age was 67 ± 10 years, 39% were female, and 95% were living at home (independently or with assistance) prior to admission. One hundred thirty-eight patients (32.8%) met the frailty criteria and 283 were not frail. Compared to non-frail patients, frail patients were older, more likely to be female, had more comorbid disease and greater functional dependence, and tended to have fewer social supports.

Mortality in the ICU did not differ according to frailty, but frail patients had higher in-hospital mortality (32% vs 16%; odds ratio [OR], 1.81; 95% CI, 1.09-3.01). With multivariable analysis controlling for age, sex, comorbidities, APACHE II score, and Sequential Organ Failure Assessment (SOFA) score during the 12-month follow-up period, frailty was independently associated with all-cause mortality (48% vs 25%; hazard ratio, 1.82; 95% CI, 1.28-2.60). When the absolute frailty score was used rather than the 4-point cutoff, an increasing frailty score was independently associated with incremental mortality. Surviving patients who were frail were less likely to be living independently at home (22% vs 44%; OR, 0.35; 95% CI, 0.20-0.61), a difference that persisted through the 12-month follow-up. Health-related quality of life at 6 and 12 months was generally lower in all domains among patients who were frail, although both groups had lower scores than expected for the general population of the province.

■ COMMENTARY

Frailty is an aspect of health status that has received little attention in critical care. However, it is easy to assess on ICU admission (*see Table*), and this well-done study shows that it is strongly associated with morbidity and mortality — independently of age, comorbidities, and other variables commonly used in evaluating prognosis. As the authors point out, "the interplay of frailty and critical illness may provide an opportunity to target and evaluate interdisciplinary programs of care and rehabilitation, with the aim of improving recovery and avoiding mortality, functional dependence, reduced quality of life and added health service utilization." Aspects of critical care such as minimization of sedation, screening for delirium, nutritional support, early assessment for ventilator weaning, aggressive mobilization, and other areas currently receiving increased attention

may be especially important in patients who are frail. Routine detection of frailty when present on ICU admission, and its inclusion in care-related decision-making for patients and their families, may facilitate the setting of goals of care and other aspects of management. ■

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PHARMACOLOGY UPDATE

Tavaborole Topical Solution, 5% (Kerydin™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The first oxaborole antifungal has been approved for the treatment of fungal toenail infection. Tavaborole is a topical solution that is applied daily to the infected nail. It is marketed by Anacor Pharmaceuticals as Kerydin™.

INDICATIONS

Tavaborole is indicated for the treatment of onychomycosis of the toenail due to *Trichophyton rubrum* or *Tricophyton mentagrophytes*.[1]

DOSAGE

Apply to the affected toenail (entire toenail surface and under the tip) once daily for 48 weeks.[1] Tavaborole is available as 5% solution (10 mL).

POTENTIAL ADVANTAGES

Resistance to tavaborole after repeated exposure has not been demonstrated.[1]

POTENTIAL DISADVANTAGES

Cure rate (complete or almost complete) is low, 15-18%, after 48 weeks of application.[1]

COMMENTS

The efficacy and safety of tavaborole was evaluated in two double-blind, randomized, vehicle-controlled trials.[1] Subjects with 20-60% involvement of the toenail without dermatophyoma or lunula involvement were randomized to tavaborole applied once daily or vehicle for 48 weeks. The primary efficacy endpoint was assessed at 52 weeks. This was defined as complete cure (complete clear nail and mycological cure). Secondary endpoints included complete or almost complete cure (mycological cure and ≤ 10% involvement in affected toenail) and mycological cure. Complete cure was observed in 6.5% in study one and 9.1% in the second trial. The values for vehicle were 0.5% and 1.5%, respectively. The percentages for complete or almost complete cure were 15.3% and 17.9% vs 1.5% and 3.9%, respectively. The percentages for mycological cure were 31.1% and 35.9% vs 7.2% and 12.2%, respectively. Adverse events were minimal (< 3%); these include application site exfoliation, ingrown toenail, site erythema, and dermatitis.[1]

CLINICAL IMPLICATIONS

Onychomycosis is a common fungal infection of the nail and nail bed. Treatment choice depends on the number of nails affected and severity of the infection. Systemic treatment is recommended for more serious forms, while superficial onychomycosis and infections limited to distal nails can be treated with topical agents. Currently available agents include ciclopirox olamine 8% and efinaconazole 10%.[2] There are currently no published studies comparing tavaborole and ciclopirox or efinaconazole; however, in similar study design and duration of treatment in subjects with similar degree of nail involvement, the complete cure rate for ciclopirox was 5.5% and 8.5% in two studies compared to 0.9% and 0% for the vehicle.[3] For efinaconazole, cure rates were 15.2% and 17.8% compared to 5.5% and 3.3% for the vehicle.[4] Therefore, tavaborole does not appear to offer any clinical advantage over existing therapy. The cost was not available at the time of this review. ■

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By Louis Kuritzky, MD

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Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Exercise for Depression

Source: Cooney G, et al. *JAMA* 2014;311:2432-2433.

Common sense would predict that exercise might be beneficial for persons with depression, but since our simple intuitions have not always been confirmed by clinical data, it is nice to see data that say "Yes, your common sense was correct. Exercise is beneficial for depression."

Cooney et al reviewed clinical trials that compared exercise with either no treatment or a control for study subjects with depression. Because different clinical trials use different depression scales, results from different trials were converted to a single metric to standardize comparisons. To make the outcomes more clinically relevant, degree of change was quantified as small, moderate, or large.

Although not all trials found a favorable effect of exercise on depression — and one trial actually reported a detrimental effect — the meta-analysis of the data found an overall moderate, favorable effect of exercise compared to control, equivalent to an approximately 5-point reduction on the Beck Depression Inventory.

The data were not sufficient to distinguish a particular type (e.g., aerobic vs non-aerobic), intensity, or duration of exercise needed to achieve a favorable impact. Nonetheless, some national guidelines already include recommendations for exercise as a treatment for mild-to-moderate depression (NICE: National Institute for Health and Clinical Excellence Guideline from the United Kingdom). Patients might be more motivated to consider exercise as a respectable treatment if they understand that favorable results are supported by scientific data. ■

A Potential New Fix for Opioid-Induced Constipation

Source: Chey WD, et al. *N Engl J Med* 2014;370:2387-2396.

Most of the commonplace adverse effects associated with opioid analgesia are transient. Constipation, unfortunately in addition to being one of the most common adverse effects of opioids, is also the most persistent. Mu receptors in the enteric nervous system (the colon has a brain, you say? Who knew!?) have a critical responsibility for controlling active propulsive activity of the colonic musculature: Activation of the mu receptor *suppresses* propulsive activity. Since all traditional opioids possess potent mu receptor agonist activity, suppression of colonic propulsive activity is routinely seen during opioid treatment, and the bowel does not appear to develop much tolerance to this effect.

Naloxegol is an oral mu receptor *antagonist* awaiting FDA approval in the United States. Because it is only effective at *peripheral* opioid receptor sites (e.g., colon) and not at *central* mu receptor sites (i.e., the CNS), it should not induce opioid withdrawal or reduce the efficacy of opioid analgesia. Data published from two randomized, double-blind, placebo-controlled clinical trials support the efficacy and tolerability of naloxegol. By intention-to-treat analysis, naloxegol provided a statistically significant and clinically meaningful sustained increase in frequency of bowel movements over a 12-week opioid treatment period compared to placebo. The drug was well tolerated. Although there are other mu receptor antagonists on the market — one is parenteral and the other is indicated only for postoperative ileus — it would be nice to have an orally active agent for patients treated with chronic opioids. ■

BP Lowering Effects of SGLT2 Inhibitors

Source: Oliva RV, Bakris GL. *J Am Soc Hypertens* 2014;8:330-339.

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are the newest class of agents available to treat diabetes. In the United States, only canagliflozin and dapagliflozin are FDA approved. SGLT2 inhibitors work by blocking the receptors in the proximal renal tubules from reabsorbing glucose back into circulation. As a result, glucose is excreted in the urine, calories are lost from the body, and we see not only reductions in plasma glucose and A1c, but reduced body weight and reduced blood pressure (BP).

BP reduction is critical in diabetics, who suffer a greater burden of cardiovascular (CV) disease than non-diabetics and worse outcomes when CV events occur. Currently, less than 50% of diabetics with hypertension have attained BP control.

A meta-analysis of placebo-controlled trials (n = 21 trials) with SGLT2 inhibitors found a mean change in systolic BP of approximately 4 mmHg. While at first glance this might seem small, remember that the patient populations selected for SGLT2 treatment were based on presence of diabetes, not hypertension, so the mean baseline BP levels in these trials would not reach the threshold for the diagnosis of hypertension.

SGLT2 inhibitors do not work to reduce glucose in persons with significant CKD (GFR < 45-60 mL/min) because they are dependent on good glomerular filtration rates to induce meaningful amounts of urinary glucose excretion. It is heartening to see a class of diabetic pharmacotherapy that not only produces improved glycemia, but also is associated with weight reduction and lower systolic BP. ■

Is This a Normal ECG?

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

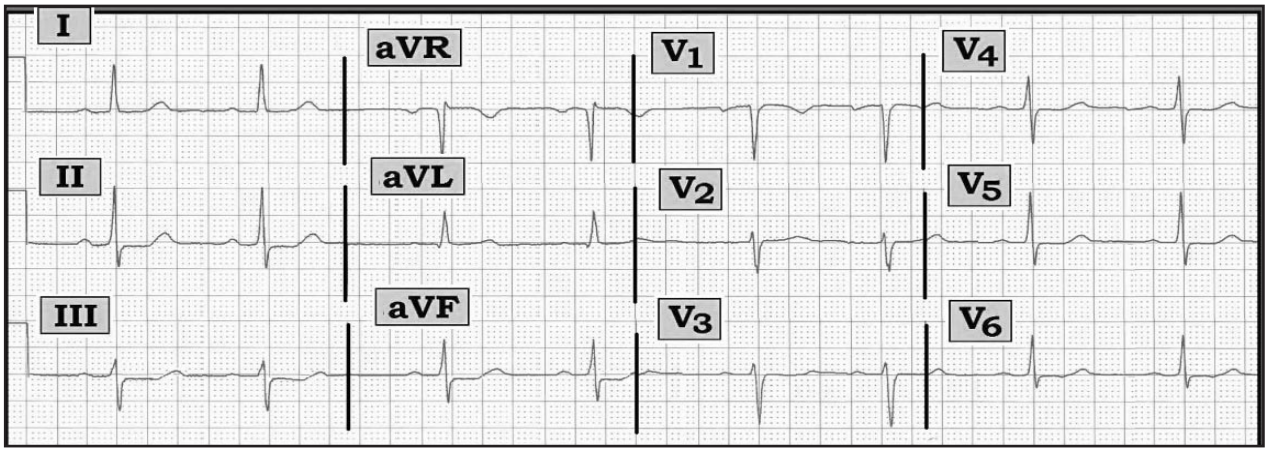

Figure — ECG from a patient with atypical chest pain.

Scenario: The ECG in the Figure was obtained from a patient with *atypical* chest pain. Is this a normal ECG? If not, *why not?*

Interpretation: The rhythm is sinus bradycardia and arrhythmia. The PR, QRS, and QT intervals are all normal. The axis is +30 degrees. There is no chamber enlargement.

Regarding Q-R-S-T Changes — A small and narrow q wave is seen in lead aVL. Transition is slightly delayed, with the R wave only becoming taller than the S wave between lead V4-to-V5. The most remarkable finding on this ECG is ST segment *flattening* with slight ST depression in multiple leads.

It should be emphasized that the *amount* of actual ST segment depression on this tracing is minimal. It is no more than 1 mm in the inferior leads. That said, there is no denying that some ST segment depression is present. Even in leads in which there is no ST depression at all (i.e., in leads V2 through V6), ST-T waves are not normal. Instead, there is *subtle-but-real* ST segment straightening in the precordial chest leads, whereas there should normally be a smooth, gradual transition between the end of the ST segment and the beginning of the T wave.

Bottom Line: This ECG is not normal. Instead, there is diffuse nonspecific ST segment flattening and slight ST depression. These changes are subtle but real. Clinical correlation is essential for knowing how to interpret this ECG finding. This patient may have coronary disease — possibly even severe coronary disease with ischemia. On the other hand, these changes are not acute and they could be due in part or in combination to any of the other potential causes of ST depression (drug effect, electrolyte disorder, hyperventilation, acutely ill patient, etc.). We simply cannot tell on the basis of this single ECG. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. The risk of developing atrial fibrillation:

a. is not increased by the use of bisphosphonates.
b. is increased by the use of intravenous bisphosphonates but not by oral bisphosphonates.
c. is increased by the use of oral or intravenous bisphosphonates.
d. None of the above

2. Which of the following statements regarding the risk of hand contamination with *C. difficile* spores among health care workers caring for patients with *C. difficile* infection is true?

a. Contact precautions offer 100% protection against hand contamination.
b. Hand contamination occurred in some health care workers despite glove use.
c. Hand contamination occurred among health care workers who cared for patients without *C. difficile* infection.
d. Hand contamination only occurred when gross fecal contamination was observed.

3. The following were all associated with a higher risk of hand contamination *except*:

a. a higher number of patient contacts.
b. a higher number of high-risk contact activities.
c. a longer exposure to high-risk contact activities.
d. at least one contact without gloves.
e. washing hands with soap and water prior to leaving the room.

4. Among patients over 50 who were admitted to the ICU, being assessed as "frail" (with a rating of ≥ 5 on the clinical frailty scale) was associated with which of the following?

a. Increased in-hospital mortality
b. Increased overall mortality over the next 12 months
c. Decreased likelihood of living independently at home after discharge
d. All of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Fibromyalgia and non-celiac gluten sensitivity: A description with remission of fibromyalgia

Vitamin D and mortality: Meta-analysis of data from a large consortium of cohort studies from Europe and the United States