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Clostridium difficile Transmission: It's Complicated

ABSTRACT & COMMENTARY

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships relevant to this field of study. This article originally appeared in the November 2013 issue of Infectious Disease Alert.

Synopsis: *This new study provides evidence that the widely accepted paradigm of horizontal Clostridium difficile transmission may not be valid.*

Source: Eyre DW, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med* 2013;369:1195-1205.

THE PREVAILING THEORY OF *CLOSTRIDIUM DIFFICILE* TRANSMISSION IS THAT most cases occur after recent exposure to symptomatic patients in health care settings. Infected patients are known to shed large numbers of *C. difficile* spores and current infection control recommendations focus on preventing spore transmission from the environment through contact precautions and decontamination of surfaces and equipment. However, the rate of *C. difficile* infection (CDI) continues to increase, bringing into question the effectiveness of these methods.

A new study by Eyre and colleagues provides evidence that the widely accepted paradigm of horizontal *C. difficile* transmission may not be valid. Over a period of 3.6 years, the investigators performed whole genome sequencing on more than 1200 clinical isolates of *C. difficile* from the Oxford University Hospitals. Any two cases were considered to be linked if they met two conditions: no more than two single-nucleotide variants (SNVs), and the patients had direct or indirect contact while one was symptomatic or contact occurred within a 12-week incubation period.

The analysis determined only 35% of the isolates were genetically linked to a prior case, while 45% had more than 10 SNVs and therefore

were not related. Patients with genetically linked isolates tended to be older than those with genetically distinct isolates (median age 81 years vs 76 years, respectively; $P < 0.001$). Moreover, 38% of the linked cases had ward contact with the previous genetically related case while 9% shared the same time in the hospital but were never on the same ward. Interestingly, no hospital-based contact could be established for 46% of the patients, implying diverse sources of acquisition. For instance, some of the patients were in the same medical practice (10%) or lived in the same postal-code district (11%) as previous cases, but no pairs of patients with two or fewer SNVs attended the same outpatient clinic on the same day. Among the 45% of cases that represented transmission from sources other than symptomatic cases, it is reasonable to conclude their CDI was acquired from either asymptomatic individuals or some other environmental reservoir (i.e. food, animals, or surfaces).

There are a few limitations to the study that require mention. First, the toxin testing used by Eyre and colleagues has been largely supplanted by more sensitive assays (e.g., polymerase chain reaction or nucleic acid tests), which probably led to an underestimation of *C. difficile* incidence in the local regions. Second, the institutions that participated in the study housed patients in four-bed bays, an arrangement that is unusual in the United States. Since the majority of patients in U.S. hospitals are in private rooms that afford less opportunity for patient-to-patient contact, the rate of *C. difficile* transmission is likely to be different between the two countries. Third, the study was conducted during a period when infection control precautions to limit the spread of *C. difficile* were widely practiced, which likely reduced the impact of symptomatic patients. Finally, it is possible that *C. difficile* has other still-unidentified reservoirs in the environment or hospitals that are important for transmission. In the study, the authors did not perform whole genome sequencing on any strains from extended-care facilities, which are known to be sources for outbreaks of *C. difficile*.

■ COMMENTARY

This study is significant because it provides evidence that in a majority of cases, CDI is not transmitted by symptomatic patients. Instead, asymptomatic individuals or other sources are likely to be the main perpetrators. This finding compels us to re-examine infection control protocols whose goal is to limit the transmission of multidrug-resistant pathogens like *C. difficile*. This is not to say we should abandon basic control methods since the infrequent transmission from symptomatic patients in the study hospitals may attest to their effectiveness. Rather, future studies that elucidate novel routes of transmission can identify currently unknown sources of CDI. For example, should all patients who are admitted to the hospital be screened for *C. difficile*? If so, what should happen to asymptomatic carriers especially since isolation in general is unpopular with patients, their families, and health care workers?

Another takeaway point from this study is that perhaps more emphasis should be placed on minimizing disruptions to the gut microbiome and its restoration (i.e., through probiotics) should be a priority. Although physicians and the public already have more than enough reasons to limit the use of unnecessary antibiotics, the threat of acquiring CDI is a valid concern and should be taken into consideration whenever these agents are prescribed. As Eyre et al note, the rate of fluoroquinolone and cephalosporin usage in the UK fell between 2006 and 2009, and during this period, active restriction of these agents in one Scottish hospital resulted in a relative reduction of 77% in the incidence of CDI. Thus, reducing the susceptibility of patients to CDI may be more effective than lowering transmission rates. Finally, this study demonstrated the usefulness of whole genome sequencing in determining the transmission of one major disease and this method holds great promise for uncovering the mechanisms of transmission for other serious pathogens. ■

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Headaches – A Hidden Disability Associated with Seizures

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

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Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim and Bayer, and is on the speakers bureau for Boehringer Ingelheim. This article originally appeared in the November 2013 issue of Neurology Alert.

Synopsis: *Periictal headaches are frequent, severe, and undertreated, and can be predicted by younger age at epilepsy onset, drug polytherapy, and tonic-clonic generalized seizures.*

Source: Duchaczek B, et al. Interictal and periictal headache in patients with epilepsy. *Eur J Neurol* 2013;20:1360-1366.

All patients aged 18 years or older with epilepsy or one unprovoked epileptic seizure, who were seen in the tertiary epilepsy outpatient clinic of the Charité University Hospital between October 2006 and December 2007, underwent a semi-structured interview to determine the prevalence of interictal (IIH) and periictal (PIH) headache. Headaches that occurred within 1 year before or after an epileptic seizure were defined as IIH. PIHs were temporally divided into preictal (occurring until the onset of a seizure or beginning at least 24 hours before seizure), ictal (during a seizure without loss of consciousness), and postictal (occurring with the end of the seizure) headaches. IIH was considered to be migraine, tension-type headache, and "other" headache. PIHs were migrainous or tension-type headaches.

A total of 201 patients (median, 42 years; range, 18-83 years), including 95 (47.3%) female patients, were interviewed. Headaches were reported by 113 patients (56.2%) with migraine in 10.9% and tension-type headache in 19.4%. There were 69 patients (34.3%) suffering from IIH, 71 (35.3%) from PIH, and 27 (13.4%) from both headache types. Out of 69 patients with IIH, 22 (31.9%) suffered from migraine, 39 (56.5%) from tension-type headaches, and 10 (14.5%) from other types, with two patients reporting both migraine and tension-type headache. The vast majority of PIHs occurred postictally with either migrainous or tension-type headache. Analgesic treatment of IIH was more common than acute treatment of PIH. Multivariate analysis identified female sex as the only independent predictor of IIH, and low age at epilepsy onset and antiepileptic polytherapy as independent predictors of PIH. PIH was significantly associated with generalized tonic-clonic seizures. The vast majority of PIH occurred postictally and had either migrainous or tension-type headache-like characteristics. This study found that while IIH, and in particular migraine, did not occur more often in patients with epilepsy than expected in the general population, PIH occurred in more than a third of patients with epilepsy.

■ COMMENTARY

With headache being a virtually universal experience, an overlap between primary headaches (migraine and tension-type headaches) and other neurological diseases is to be expected. Determining whether there is an increased prevalence of headache in patients with a neurological disease, especially when the neurological disease and headaches occur in populations of predominantly the same age and gender, can be problematic. In this study of IIH in patients with epilepsy, the prevalence of tension-type headache (19%) and migraine (11%) was less than the prevalence predicted from epidemiological studies performed on the general population. More information is needed to analyze this finding, including whether the choice of antiepileptic drug (AED) could impact the prevalence of migraine headaches in an epileptic population.

PIH was frequently reported by patients with multiple seizures and was infrequently treated, even with over-the-counter analgesic medication. The disability associated with the actual seizure is often overt, but the head pain around the ictal event, while less evident to the health care provider, may be equally debilitating. The use of acute pain medications after a seizure should be encouraged in those with PIH. The impact of headaches associated with a seizure may dictate the choice of AED, with the possibility of dual therapeutic benefit. ■

Botulinum Toxin for Postherpetic Neuralgia

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study. This article originally appeared in the November 2013 issue of Neurology Alert.

Synopsis: *In a small, placebo-controlled trial, botulinum toxin treatment showed a significant benefit for postherpetic neuralgia.*

Source: Apalla Z, et al. Botulinum toxin A in postherpetic neuralgia: A parallel, randomized, double-blind, single-dose, placebo-controlled trial. *Clin J Pain* 2013;29:857-864.

Rare in children and those under 60 years of age, postherpetic neuralgia (PHN) causes persistent pain for months to years following resolution of the acute zoster rash, occurring in 6.9% of patients 60-69 years of age and in 18.5% of those 70 years or older, with increasing severity and persistence of PHN associated with advancing age. Current treatment options include tricyclic antidepressants, anticonvulsants, opioids, topical creams such as capsaicin or lidocaine, and intrathecal glucocorticoids. Botulinum toxin appears to be another, less invasive and reasonable, option.

Between April and November 2009, 30 adults, aged ≥ 18 years, with PHN of more than 3 months' duration, were enrolled in a 4-week, randomized, double-blinded, two-arm, single-dose, placebo-controlled study examining the safety, efficacy, and tolerability of botulinum toxin A (BTX-A) for PHN. Complete responders were subsequently maintained in an open-label, 20-week follow-up phase to evaluate continued pain control. Study enrollment required a baseline pain score of at least 7, as measured by a visual analogue scale (VAS), and patients were excluded if they demonstrated cranial nerve involvement, skin disorders that might interfere with BTX-A injection, or severe non-PHN pain disorders that could interfere with pain measurements. Dose of BTX-A totaled 100 IU, and was injected over the affected area in a checkerboard fashion, with each patient receiving a total of 40 injections. Patients assessed their pain severity daily for 2 weeks on waking in the morning, using a VAS (0-10), and then every 2 weeks for 12 weeks, followed by every 4 weeks for 10 weeks. Quality of sleep was assessed using a five-item questionnaire, encompassing overall sleep quality, number of nights unable to sleep due to pain, number of times sleep was interrupted at night by pain, number of continuous hours of nightly sleep, and length of time until falling asleep. VAS score reduction was the primary outcome measure, and secondary outcome measures included sleep score improvement and maintenance of > 50% improvement of VAS score after treatment. Statistical analysis encompassed Fisher exact test and, where appropriate, Mann-Whitney U test or the Pearson X2 test.

Thirty PHN patients were enrolled, mean age was 73.2 years, with 15 enrolled in each arm. Of those receiving BTX-A, 13 patients (87%) experienced at least 50% reduction in VAS pain score, compared to none of the placebo patients, with improvement achieved within the first 2 weeks and maintained over a median of 16 weeks. Sleep score similarly improved within 2 weeks among BTX-A recipients and continued until week 16. BTX-A was well tolerated, with no patient discontinuing treatment or experiencing systemic side effects. Pain during injection was seen equally in both the BTX-A and placebo arms, was transient, and resolved within 24 hours. The authors concluded that BTX-A is safe and effective for PHN.

■ **COMMENTARY**

Initially introduced in the late 1970s for focal dystonias and strabismus, botulinum toxin presently enjoys widespread use for everything from anal spasm to vaginismus, including autonomic disorders such as hyperhidrosis, cosmetically troubling "crows-feet" and other troublesome facial lines, and even pain syndromes such as migraine and tension headaches. Best known for inhibiting acetylcholine release at the neuromuscular junction by interfering with calcium regulated synaptic vesicle exocytosis, its pain-modulating qualities appear to be independent of its effect on muscle contraction, suggesting alternate mechanisms for its analgesic capabilities. Evidence suggests that it both reduces Ia afferent fiber traffic and inhibits release of substance P, a neuropeptide with a significant role in pain perception and neurogenic inflammation. Formalin-induced pain in experimental animals, which results from direct stimulation of nociceptors followed by inflammation, rather than from muscle tension, is also reduced by botulinum toxin, supporting a direct effect on the nociceptor system, in addition to its neuromuscular junctional effect. ■

Cancer Survivorship… The Marriage Effect?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study. This article originally appeared in the November 2013 issue of OB/GYN Clinical Alert.

Synopsis: *Compared to cancer patients who were never married, divorced, widowed, or separated, married patients are significantly more likely to present at an earlier stage, undergo therapy with definitive or curative intent, and live longer among each of the 10 most common cancers killers in the United States. The data suggest the effect is rooted in better social support mechanisms among this cohort and highlight a modifiable "at-risk" population.*

Source: Aizer AA, et al. Marital status and survival in patients with cancer. *J Clin Oncol* 2013;31:3869-3876.

The positive effect of marriage on cancer survivorship previously has been reported but is not universal among various investigations.[1,2] The authors set out to examine the impact of marital status on stage at diagnosis, use of definitive therapy, and cancer-specific mortality between each of the 10 leading causes of cancer-related death in the United States. To interrogate a sample large enough to adjust for the various covariates, they identified more than 1.2 million cancer patients registered in the Surveillance, Epidemiology and End Results (SEER) program who were diagnosed between 2004 and 2008. Ten primary tumor sites (lung, colorectal, breast, pancreatic, prostate, liver/intrahepatic bile duct, non-Hodgkin lymphoma, head/neck, ovarian, or esophageal cancer) were addressed, as they represented the most common diagnoses associated with cancer-specific morality. After eliminating cases with inadequate clinical and follow-up information, 734,889 patients were available for analysis. The authors found that married patients were less likely to present with metastatic disease (adjusted odds ratio [OR], 0.83; 95% confidence interval [CI], 0.82-0.84; $P < 0.001$), more likely to receive definitive therapy (adjusted OR, 1.53; 95% CI, 1.51-1.56; $P < 0.001$), and less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79-0.81; $P < 0.001$) than unmarried patients. These associations remained significant when each individual cancer was analyzed ($P < 0.05$ for all endpoints for each malignancy) and regardless of unmarried status ($P < 0.001$ for each unmarried category). The benefit associated with marriage was greater in males than females for all outcome measures analyzed ($P < 0.001$ in all cases). For prostate, breast, colorectal, esophageal, and head/neck cancers, the survival benefit associated with marriage was larger than the published survival benefit of chemotherapy. The authors concluded that unmarried patients are at significantly higher risk of presentation with metastatic cancer, undertreatment, and death resulting from their cancer, even after adjusting for known confounders. This study highlights the potentially significant impact that social support can have on cancer detection, treatment, and survival.

■ COMMENTARY

"My wife says I never listen to her…at least I think that's what she says…."

The impact of marriage on survivorship in cancer patients has been extensively examined in previous reports, but with inconclusive independent results. Most have shown a benefit but have been confounded by small samples size for individual malignancies, regionality, lack of information regarding follow-up, and survival not linked to cancer-specific events. However, the current study's design and analysis, while not optimal (e.g., a randomized trial), does provide some confidence the association is credible. This comes from several considerations. First, the sample was based on cancer-specific survivorship, that is, those cases in which death was recorded as a cancer event. This type of analysis censors patients who die before progression or from causes not related to cancer. In treatment trials, this endpoint is often considered to be biased because elderly patients are more likely to die of intercurrent disease leading to extensive censoring. However, for the current analysis, it provides cleaner data to assess the effect of the variable (marriage at diagnosis) on cause-specific outcomes across a variety of tumors. The second aspect affording credibility to this study's hypothesis-generating suppositions is the multi-regional patient inclusion. The SEER database captures more than 95% of the incident cancers from registries representing more than a quarter of the U.S. population. There are well-documented deficiencies in this database (e.g., no pathology review, lack of information regarding chemotherapy, oversimplified, and lack of confirmation of staging), but the demographics, diagnoses, stage category, some treatment, and outcomes recorded have been continually validated and updated for years. Third, the sample is large enough to consider important covariates such as, age, race, gender, residence, income, education, tumor and nodal stage, and treatment. In the context of marriage, these are important variables since married cancer patients tend to be younger, have higher incomes and education level, may have broader and better access to health care, and live in rural homesteads with larger family support mechanisms.[3] Considering these factors, marriage was still significantly protective and remained so for the 10 tumor types examined and relative to each unmarried category. Further, the effect in many tumor types (prostate, breast, colorectal, esophageal, and head/neck) was stronger than the impact of chemotherapy.

The primary takeaway message from this article, and others on the topic, is that marriage provides a critical internal social support system that is less often present among patients who are unmarried — these patients represent a risk group that deserves attention. While the quality of marriage among those married and the contribution of live-in unmarried cohabiters could not be directly assessed, it appears that marriage at the time of diagnosis is associated with important primary treatment variables that would be expected to result in better outcomes. For instance, most primary outcome measures, such as overall survival, progression-free survival, and objective response, are directly associated with tumor stage at presentation; earlier stage = better outcomes. Thus, tumors in which symptomatology may be reflective of an early-stage diagnosis (e.g., epistaxis in head and neck cancer) are more likely to be associated with better outcomes if a partner encourages ("nagging") a doctor's appointment at first occurrence.[4] Earlier stage at presentation would also increase the likelihood of defini-

tive treatment options and increase the odds of finishing a prescribed treatment plan. Each of these factors has been broadly associated with more favorable survival in a variety of cancers. In ovarian cancer, symptomatology is not associated with earlier stage at presentation, but may be associated with lower metastatic tumor burden, affording a higher likelihood to undergo primary surgical debulking, to have a better cytoreduction outcome, and complete definitive adjuvant therapy. Finally, chronic stress has been implicated as negatively impacting cancer survivorship, particularly in regard to immune function and the tumor microenvironment, where stress is associated with accelerated angiogenesis and immune escape.[5,6] The hypothesis that married patients are less likely to suffer chronic stress and depression than their unmarried counterparts has been previously raised and may contribute to the study's findings.

So how can this information be leveraged? The knowledge that unmarried cancer patients represent an at-risk group provides an opportunity to develop and evaluate social support mechanisms that can act as surrogates for a live-in partner. Most cancer centers have regular patient supportive-expressive group therapy sessions. However, their impact on survival has been mixed in the few randomized controlled studies that have been conducted.7,8 Nevertheless, comprehensive programs that provide not only social-expressive opportunities but also assessment/management of depression and anxiety and assistance with decision making represent the best opportunity to close the "survival gap" observed in unmarried individuals. Increased awareness and assessment of depression/anxiety should be afforded to all cancer patients. However, knowing the risks that may further impact and complicate a patient's treatment program, clinicians are encouraged to thoroughly evaluate the social support structure of unmarried patients at presentation and during their follow-up. ■

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Pharmacology Update

Luliconazole Cream 1% (Luzu®)

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.

A NEW AZOLE ANTIFUNGAL CREAM HAS BEEN APPROVED FOR the treatment of Athlete's foot, jock itch, and ringworm infection. Luliconazole is manufactured by Medicis and marketed by Valeant Pharmaceuticals as Luzu.

Indications

Luliconazole is indicated for the topical treatment of interdigital tinea pedis (Athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) caused by *Trichophyton rubrum* and *Epidermophyton floccosum* in adults.[1]

Dosage

For tinea pedis, the cream should be applied to the affected and immediate surrounding areas once daily for 2 weeks.[1] For tinea cruris and tinea corporis, the cream should be applied once daily for 1 week.

Luliconazole is available as a 1% cream in 30 g and 60 g tubes.

Potential Advantages

Luliconazole is the first topical azole antifungal to be approved for once-daily, 1-week treatment for tinea cruris and tinea corporis. Luliconazole's activity in vitro and in vivo is higher than terbinafine.[2,3,4]

Potential Disadvantages

Contact dermatitis and cellulitis have been reported

during post marketed use.[1] However, direct causality has not been established. It is available only by prescription compared to most commonly used topical antifungals that are over the counter.

Comments

The safety and efficacy of luliconazole in tinea pedis were evaluated in two randomized, double-blind, vehicle-controlled trials in 423 subjects. Subjects were randomized to luliconazole 1% or vehicle applied once daily for 14 days. Approximately 1 inch of cream was applied to all interdigital web spaces. The primary efficacy endpoint was complete clearance (clinical and mycological cure) at 4 weeks post-treatment. Complete clearance (vs vehicle) occurred in 26% (vs 2%) and 14% (vs 3%) in the two studies, respectively. Mycological cure rate was 62% (vs 18%) and 56% (vs 27%). For the treatment of tinea cruris, subjects were randomized to luliconazole 1% (n = 165) or vehicle (n = 91) applied once daily for 7 days. Complete clearance at 3 weeks post treatment was 21% for luliconazole (vs 4%). Mycological cure was 78% (vs 45%). Luliconazole cream is well tolerated with application site reactions occurring in less than 1% of subjects. A 4-week treatment of tinea pedis achieved complete clearance of 45.7% 2-weeks post treatment compared to 26.8% at 2 weeks post treatment after a 2-week treatment. Vehicle responses were 9.1% and 10%, respectively.[5]

Clinical Implications

Luliconazole cream is the newest azole antifungal to be approved. It has been available in Japan since 2005. It is a potent antifungal that is approved for a shorter treatment course for tinea cruris and tinea corporis than current commonly used antifungals such as terbinafine. Clinical cure (absence of erythema, scaling, and pruritus), however, is only 15-29% for tinea pedis and 24% for tinea cruris. A longer treatment appears to improve effectiveness. Luliconazole as a 10% solution has shown accumulation in the nail and is being studied for mild-to-moderate onychomycosis.[6,7] Unlike other topical antifungals that are available over the counter, luliconazole is only available with a prescription. The wholesale cost of luliconazole cream was not available at the time of this review. ■

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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.

CME Questions

1. Which of the following is correct with regard to the study of *Clostridium difficile* transmission in Oxford University Hospitals?

a. All isolates were genetically linked.
b. Only approximately 5% of isolates were genetically linked.
c. Approximately one-third of isolates were genetically linked.
d. All patients with *C. difficile* infection were epidemiologically and genetically linked to other cases.

2. Periictal headache is associated with which of the following?

a. Male gender
b. Recent onset of seizures
c. Tonic-clonic seizures
d. Antiepileptic drug monotherapy
e. Increased seizure frequency

3. Which of the following is a treatment option for postherpetic neuralgia?

a. Antidepressants
b. Topical creams such as capsaicin or lidocaine
c. Intrathecal glucocorticoids
d. Botulinum toxin A injections
e. All of the above

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

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

ACE + ARB for Kidney Disease: Too Much of a Good Thing

Source: Fried LF, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892-1903.

Supranormal excretion of albumin in the urine portends decline in renal function. Although transient increases in urine protein may be seen in otherwise healthy individuals with fever or vigorous physical exercise, sustained elevations of albumin are a marker for chronic kidney disease (CKD). To date, numerous clinical trials have shown that treatment with angiotensin-converting enzyme (ACE) inhibitors *or* angiotensin-receptor blockers (ARBs) can have favorable effects on urinary protein excretion, whether the patient has underlying hypertension. There has been controversy over whether combined ACE inhibitors + ARBs might be more beneficial than either agent alone. A recent large clinical trial (ONTARGET) — although not powered to determine renal outcomes — found a concerning increase in endstage renal disease in study subjects treated with ACE inhibitors + ARBs.

The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study enrolled CKD patients with proteinuria, all of whom were treated with losartan (ARB), and half of whom were randomized to the addition of lisinopril. The primary endpoint of the study was change in glomerular filtration rate.

The study was discontinued prematurely by recommendation of the data and safety monitoring committee based on the burden of serious adverse events (e.g., hyperkalemia, acute kidney injury) combined with the low likelihood of a favorable effect on the primary endpoint. The prevailing opinion that ACE inhibitors + ARBs are not a favorable choice for addressing proteinuria is now further substantiated. ■

Linagliptin in Seniors with Type 2 Diabetes

Source: Barnett AH, et al. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: A randomised, double-blind, placebo-controlled trial. *Lancet* 2013;382:1413-1423.

It may come as a surprise that even though approximately 25% of adults older than age 65 have diabetes, this age group is dramatically under-represented in clinical trials. Indeed, almost one-third of interventional trials have age > 65 as an exclusion! Therefore, it is heartening to see a clinical trial specifically addressing seniors (mean age 75 years) with type 2 diabetes (DM2).

Barnett et al studied DM2 patients who were not at goal (mean A1c = 7.8%) despite treatment with metformin, sulfonylurea, and basal insulin (alone or in combination). Study subjects were randomized to linagliptin 5 mg/d or placebo, and followed for 6 months. The primary endpoint was change in A1c.

Treatment with linagliptin was both effective (mean placebo-adjusted A1c decline = -0.64%) and safe. No serious adverse events related to the study drug occurred; although there was a trend for more hypoglycemic events in the linagliptin arm of the study, the results did not reach statistical significance.

It is reassuring to see that seniors can attain greater glucose control in a safe fashion. [Note: this was an industry sponsored study by Boehringer Ingelheim, makers of linagliptin.] ■

Sorting Out the Best Candidates for Successful Warfarin Use

Source: Apostolakis S, et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The SAMe-TT2R2 Score. *Chest* 2013;144:1555-1563.

Risk reduction for stroke afforded by warfarin treatment in atrial fibrillation (AF) is impressive: Clinical trials consistently show approximately two-thirds reduction in risk of stroke compared to placebo. Additionally, overall mortality is reduced by more than 25%. Because efficacy is closely linked to time *in* the therapeutic range, and toxicity is equally closely linked to time *outside* the therapeutic range, it is valuable to see if we can identify clinical characteristics that predict which patients are most likely to maintain adequate anticoagulation.

With data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial, Apostolakis et al derived the acronym "SAMe-T_2TR_2" using the metrics of female sex, age < 60, minority ethnicity, > 2 comorbidities, medication regimen (beta-blocker, verapamil, or amiodarone), and tobacco use. The SAMe-T_2TR_2 score would stratify patients into low risk for suboptimal control (score 0-1) vs at risk for suboptimal control (score > 2).

Newer antithrombotic agents (apixaban, dabigatran, rivaroxaban) offer little efficacy advantage over warfarin for patients who can maintain anticoagulation within the therapeutic range more than 70% of the time. Stratification tools that are comprised of readily identified clinical elements may help us suggest the most appropriate therapeutic choices. ■

In Future Issues: Compression Stockings to Prevent Post-thrombotic Syndrome