Journal of Antimicrobial Chemotherapy (2006) **58**, 645–650
doi:10.1093/jac/dkl279
Advance Access publication 27 June 2006

JAC

Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections

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Received 17 April 2006; returned 18 May 2006; revised 31 May 2006; accepted 8 June 2006

***Background*: Increased incidence of methicillin-resistant *Staphylococcus* species has required some hospitals to choose vancomycin for surgical prophylaxis. Guidelines for appropriate timing of vancomycin prophylaxis state that the infusion should begin within 120 min before the first surgical incision. However, no studies have investigated the proper timing of vancomycin prophylaxis in relationship to surgical site infections (SSI). The objective of the present study was to assess the effect of vancomycin prophylaxis timing in relation to the first surgical incision on the incidence of SSI.**

***Methods*: We prospectively monitored vancomycin prophylaxis timing and incidence of SSI in 2048 patients undergoing coronary bypass graft or valve replacement surgery. The timing of vancomycin was categorized into five groups based on the relation between the start of the infusion and the surgical cut time. Study hypotheses were tested using logistic analysis and further validated using a Heckman two-stage model.**

***Results*: The incidence of SSI were lowest in the 176 patients given vancomycin between 16 and 60 min before the surgical incision (3.4%) compared with 15 patients given vancomycin between 0 and 15 min [26.7%; relative risk (RR): 7.8; 95% CI: 2.5–24.7], 888 patients given vancomycin between 61 and 120 min (7.7%; RR: 2.2; 95% CI: 0.99–5.09), 700 patients given vancomycin between 121 and 180 min (6.9%; RR: 2.0; 95% CI: 0.87–4.62) or 269 patients given vancomycin >180 min (7.8%; RR: 2.3; 95% CI: 0.94–5.56) ($P = 0.0119$ by χ^2 analysis). Stepwise logistic regression analysis and a Heckman two-stage model confirmed that vancomycin administration between 16 and 60 min before the first surgical incision was associated with the lowest incidence of SSI.**

***Conclusions*: Vancomycin administration within 16–60 min before the first surgical incision reduced the risk of SSI in cardiac surgery patients.**

Keywords: antibiotic surgical prophylaxis, surgical wound infection/prevention and control, antibacterial agents/administration and dosage, prospective study

Introduction

Antibiotic prophylaxis has been routinely used for more than 25 years to prevent post-operative infectious complications including surgical site infections (SSI) and bacteremia.[1–3] In cardiovascular surgery, cephalosporin antibiotics are considered the drugs of choice for surgical prophylaxis to prevent SSI as they are generally well tolerated and have broad antibacterial action against commonly isolated organisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis*.[2,4] In recent years, an increased incidence of methicillin-resistant *S. aureus* (MRSA) and the emergence of community-acquired MRSA along with high rates of methicillin-resistant *S. epidermidis* (MRSE) have required some hospitals to choose alternative antibiotics for surgical prophylaxis.[5,6] Vancomycin is most commonly recommended for surgical prophylaxis in hospitals with a high frequency of MRSA or MRSE infections although there is no consensus on the definition of a high frequency of MRSA. Routine use of

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vancomycin in other settings is generally discouraged due to the potential emergence of vancomycin-resistant *Enterococcus* (VRE) or vancomycin-resistant *S. aureus* (VRSA).[7]

In 2001, vancomycin completely replaced cefuroxime for antibiotic prophylaxis in patients undergoing cardiac surgery at a 664 bed adult tertiary care hospital located in Houston, Texas. The rationale for the use of vancomycin was increased rates of SSI along with increased prevalence of methicillin-resistant *Staphylococcus* species infections that exceeded 60% hospital-wide and more than 70% for isolates from cardiac surgery patients with SSI. Current guidelines for the appropriate timing of antibiotic prophylaxis state that the antibiotic infusion should begin within 60 min before the start of surgery based on previously published studies using cephalosporin antibiotics for surgical prophylaxis.[2,8,9] However, when vancomycin is administered, it is recommended that the infusion begin within 120 min before the incision to prevent antibiotic toxicities. However, no studies have investigated the proper timing of vancomycin in relationship to SSI or bacteraemia. Compared with the shorter half-lives of commonly used cephalosporin antibiotics such as cefazolin or cefuroxime (30 min to 2 h), vancomycin has a half-life of 5–11 h in patients with normal renal function. We hypothesized that the current recommendation to begin the infusion within 2 h of the start of surgery may possibly be extended to a longer period due to the longer half-life of vancomycin. Thus, the objective of the present study was to assess the effect of vancomycin prophylaxis timing in relation to the time of first surgical incision on the incidence of SSI.

Methods

The study was conducted at St Luke's Episcopal Hospital, a 664 bed adult tertiary care hospital located in Houston, Texas. All study procedures were approved by the hospital institutional review board. Vancomycin is used for surgical prophylaxis and is recommended to be given 1–2 h before surgery, infused over 1 h using Rely-a-Flow tubing (I Flow Corp, Lake Forest, CA, USA). Rely-a-Flow tubing uses flow control tubing instead of roller clamps to provide a fixed flow rate to help eliminate over-infusions. Patients are given one dose pre-operatively (1000 mg) and two doses post-operatively (1000 mg) every 12 h unless a drug toxicity occurs.[2] Elective surgery patients are generally admitted to a same day admission unit in the hospital for initial processing. In this unit, they are required to shower with chlorhexidine soap and undergo pre-operative blood work. From this unit, they are transferred to a pre-operative holding area for final surgical instructions before being transferred to the surgical suite. Surgery times are generally divided into first case that begins between 6:00 am and 8:00 am, second case (8:01–10:00 am), third case (10:01–12:00 pm), fourth case (12:01–2:00 pm) and non-scheduled times (2:01–5:59 am). Antibiotic prophylaxis is started in the pre-operative holding area for the first surgical case of the day and in the same day admission unit for all subsequent cases immediately prior to transferring the patient to the pre-operative holding area. A delay in antibiotic prophylaxis is generally due to the arrival of a non-elective surgical patient that postpones the elective surgery or a delay in the previous surgery being performed in the surgical suite. For most of the pre-operative areas, antibiotics are given using a bar code scanner to verify the correct identity of the patient and the drug being infused. This allows for electronic capture of antibiotic prophylaxis timing. In the remaining areas of the hospital, nurses are required to document the exact time the antibiotic infusion is started.

All patients who underwent coronary bypass graft or valve replacement surgery between June 2002 and June 2005 were prospectively monitored for the start time of vancomycin prophylaxis and development of SSI or bacteraemia. Patients were excluded if surgery was due to an infection-related diagnosis such as endocarditis, if they had undergone previous cardiac surgery within the past year or if they did not receive vancomycin prophylaxis. Demographic and surgical variables were obtained electronically from hospital and surgical databases. Underlying diseases that were known risk factors for SSI were obtained from these databases and using patient ICD9 codes supplied by medical records. Underlying diseases were classified according to ICD9 codes using the *International Classification of Diseases, tenth revision, Clinical Modification*. Patients were followed for 30 days post-operatively for development of SSI of the sternum or donor site by trained infection control personnel or infectious disease physicians using CDC criteria.[10] Briefly, infections occur within 30 days after surgery and can include the following types: (i) superficial incisional (infection above the sternum with no bony involvement); (ii) deep incisional (infection involving the sternum) and (iii) organ/space (site-specific infection, such as mediastinitis). Patients with SSI must have positive cultures of mediastinal or leg donor site fluid or tissue; evidence of infection during surgical re-exploration; or fever, chest pain or sternal instability and at least one of the following: purulent drainage from the mediastinal area, positive blood culture results and positive results of cultures from drainage fluid samples. Microbiological cultures, admission reports and surgical schedules were scanned daily for possible SSI. Diagnosis of SSI was confirmed by medical chart review, by patient examination or by discussion with the primary surgeon. Identification and susceptibility testing of pathogens from SSI was performed by the hospital clinical microbiology laboratory using automated microbiological techniques.

Patients were assigned to five groups on the basis of the relation between the start time of the vancomycin infusion and the time of the initial surgical incision. Groups were divided into vancomycin infusion begun 0–15 min before incision (group 1), 16–60 min before incision (group 2), 61–120 min before incision (group 3), 121–180 min before incision (group 4) and >180 min before incision (group 5).

Statistical analysis

All statistical analyses were performed using SAS, version 9.1 (SAS, Inc, Cary, NC, USA). Values are expressed as mean ± standard deviation for continuous variables and as a percentage of the group from which they were derived for categorical variables. All tests were two tailed, and a P value <0.05 was considered significant. The χ^2 test was used to compare rates of SSI and bacteraemia according to the vancomycin timing group. Relative risk (RR) of infection was calculated among each timing group.

A logistic regression model was developed to predict significant risk factors for SSI while controlling for other known risk factors for infection that may confound the timing results. In separate univariate analyses, risk factors for the main dependent variables and surgical site infection were performed for each covariate. RR and 95% confidence intervals (CI) were calculated for categorical variables. Fisher's exact or χ^2 tests were used for categorical variables and the Student's t-test or the Wilcoxon rank-sum test for continuous variables. Variables with a P value of <0.2 in the univariate analyses were included in the logistic regression model for the multivariable analysis. Risk factors were checked for confounding, collinearity and interaction. A backwards selection process was used to reduce the

number of covariates. Covariates with a P value <0.05 were included in the final model.

Sensitivity analysis

Because the process of assigning patients to different study groups was not random, potential selection bias among study groups due to unknown or unobserved confounders could not be completely excluded. To ensure that the study results were not significantly affected by the potential selection bias, the effect of vancomycin prophylaxis timing on the incidence of SSI was re-estimated using a two-stage Heckman model.[11,12]

In the first stage, the outcome of being included in each of the vancomycin timing groups was modelled from factors that potentially influenced treatment assignment using a probit equation. It was believed that the timing of vancomycin prophylaxis was primarily influenced by the start time of surgery as the first surgical case of the day was most likely to be given vancomycin without delay. It was also believed that the surgery starting time had little or no impact on the post-surgery patient outcomes. Therefore, the time of first surgical incision was used in the first stage model as an instrument. Other explanatory variables included patient age, gender and underlying diseases and surgery type. The vector of coefficients of explanatory variables estimated through this model was used to calculate the expected value of error (inverse Mill's Ratio). In the second stage, surgical site infection was modelled according to this estimate of the expected value of error and the covariates included in the original logistic analysis.

Results

Study population

A total of 2048 patients qualified for the study during the time period. Patients were primarily male (68%), Caucasian (53%) and aged 64 ± 12 years (mean ± SD). Coronary artery graft bypass (CAGB) surgery was most commonly performed (66%), followed by valve replacement (20%), or both CABG and valve replacement (14%). All patients had National Nosocomial Infection Surveillance (NNIS) score of 1 or 2 with the majority having NNIS score = 1 (81%) and the average operation duration was 216 ± 91 min. Comorbidities present in >10% of patients included coronary artery disease (84%), hypertension (67%), diabetes (37%), congestive heart failure (35%), unstable angina (13%), chronic obstructive pulmonary disease (12%) and obesity (12%).

Timing of vancomycin administration

Of the 2048 patients in the study, 15 (0.73%) received vancomycin 0–15 min before incision, 176 (8.6%) 16–60 min before incision, 888 (43.4%) 61–120 min before incision, 700 (34.2%) 121–180 min before incision and 269 (13.1%) >180 min before incision (Table 1). Patients scheduled for the first surgery of the day were more likely to be given vancomycin between 15 and 120 min than any other group ($P < 0.0001$) and were less likely to be given vancomycin >180 min before the incision. Fewer than 1% of patients scheduled for the first surgery of the day received vancomycin >180 min before the incision while >20% of patients in all surgical time categories received vancomycin >180 min before incision.

Surgical site infections

Of the 2048 patients in the study, 147 SSI were detected (7.2%). No outbreaks of any specific organism were noted during the study period. A total of 181 isolates were recovered from the 147 patients with SSI. All patients had at least 1 positive culture and 16 patients had ≥2 positive cultures. Of the patients 82% experienced an infection of the sternum and 18% experienced a donor site infection. The most common Gram-positive pathogens (62% of all isolates) included MSSE (24%), MSSA (18%), MRSE (13%) and MRSA (6%). The most common Gram-negative pathogens included *Enterobacter* species (12%), *Pseudomonas aeruginosa* (7%), *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* (4% each). Causative organisms for patients with multiple cultures included *S. aureus* with a Gram-negative organism ($n = 7$), coagulase-negative staphylococcus with a Gram-negative organism ($n = 7$), more than one Gram-negative organism ($n = 3$) or a Gram-negative organism with enterococcus ($n = 1$). Using the χ^2 analysis, a significant association was found between vancomycin timing and development of SSI ($P = 0.0119$) (Table 1). SSI developed in 4 of 15 (26.7%) patients who received vancomycin 0–15 min before incision, 6 of 176 (3.4%) patients who received vancomycin between 16 and 60 min before incision, 68 of 888 (7.7%) patients who received

Table 1. Temporal relationship between administration of vancomycin prophylaxis and rates of surgical site infections

Time of vancomycin administration	No. of patients	No. (%) of infections[a]	Relative risk (95% CI)	Odds ratio (95% CI)[b]
0–15 min	15	4 (26.7)	7.8 (2.5–24.7)	11.6 (2.6–52.4)[c]
16–60 min	176	6 (3.4)	1.0	1.0
61–120 min	888	68 (7.7)	2.2 (0.99–5.09)	2.3 (0.98–5.61)[d]
121–180 min	700	48 (6.9)	2.0 (0.87–4.62)	2.6 (1.1–6.2)[e]
>180 min	269	21 (7.8)	2.3 (0.94–5.56)	2.1 (0.82–5.62)[f]

[a] $P = 0.0119$ by the χ^2 analysis.
[b] Determined using multivariate logistic regression, controlling for significant covariates.
[c] $P = 0.0014$.
[d] $P = 0.056$.
[e] $P = 0.037$.
[f] $P = 0.12$.

vancomycin between 61and 120 min before incision, 48 of 700 (6.9%) patients who received vancomycin between 121 and 180 min before incision and 21 of 269 (7.8%) patients who received vancomycin >180 min before incision. There was no difference in isolation of Gram-positive compared with Gram-negative organisms based on timing of vancomycin.

Logistic regression analysis

Descriptive characteristics of study patients and their relationship to SSI are shown in Table 2. Variables with a P value <0.2 included in the logistic regression analysis included the demographics variables age, gender and race; past medical history variables atherosclerosis, coronary artery disease, chronic obstructive pulmonary disease and diabetes; and surgical variables non-elective surgery and type of surgery. In the final model, gender, underlying coronary artery disease, chronic obstructive pulmonary disease and CABG surgery with leg vein graft were not statistically significant and were excluded from the model. After controlling for these covariates, the results of two timing groups were significant in relation to the group that received vancomycin between 16 and 60 min. Compared with this group, patients who received vancomycin between 0 and 15 min before surgery had the highest risk of SSI (OR = 11.6; 95% CI = 2.6–52.4; P = 0.0014) followed by patients who received the antibiotics between 121 and 180 min before surgery (OR = 2.6; 95% CI = 1.1–6.2l; P = 0.037). Although not statistically significant, patients who received vancomycin between 61 and 120 min before the start time of surgery (OR = 2.2; 95% CI = 0.99–5.09; P = 0.056) or more than 180 min before the start time of the surgery (OR = 2.3; 95% CI = 0.82–5.62; P = 0.12) also had a higher risk of SSI compared with the group that received vancomycin between 16 and 60 min.

Table 2. Characteristics of study populations in relation to risk for surgical site infections (SSI)

Variable	SSI OR	95% CI lower	95% CI upper	P value
Demographics				
Age, years				0.19
infected	63 ± 12			
not infected	65 ± 12			
Gender, female	1.27	0.92	1.75	0.15
Race				
Caucasian	1.00			<0.001
African-American	1.01	0.88	2.50	
Hispanic	1.48	0.60	1.68	
other	0.15	0.03	0.19	
Past medical history				
Angina	1.25	0.82	1.92	0.31
Atherosclerosis	2.07	1.35	3.17	<0.01
Coronary artery disease	1.38	0.85	2.23	0.18
Congestive heart failure	1.49	1.09	2.05	0.01
Chronic obstructive pulmonary disease	0.64	0.36	1.14	0.12
Diabetes mellitus	1.62	1.19	2.22	<0.001
Hypertension	0.86	0.62	1.20	0.37
Leukaemia/lymphoma	2.05	0.56	7.46	0.29
Obesity	1.09	0.68	1.75	0.73
Peripheral vascular disease	1.31	0.63	2.70	0.47
Transplant	2.86	0.49	16.61	0.26
Solid organ cancer	0.52	0.08	3.61	0.50
Surgical variables				
NNIS score = 2	1.20	0.82	1.75	0.36
Operation duration (min)				0.44
infected	221 ± 94			
not infected	215 ± 91			
Non-elective surgery	0.48	0.20	1.20	0.10
Surgery type				
valve replacement	1.00			<0.001
CABG with leg vein	0.88	0.61	1.27	
CABG without leg vein	2.69	1.88	3.85	
Surgery time				
first case	1.00			0.52
second case	1.54	0.80	2.97	
third case	1.35	0.63	2.90	
fourth case	1.74	0.84	3.60	
other time	1.82	0.86	3.82	

NNIS, National Nosocomial Infection Surveillance.

Sensitivity analysis

The associations between different vancomycin prophylaxis timing and the risks of surgical site infection estimated from a Heckman two-stage model were very close to the results of the original logistic analysis (Table 3). Theta (error estimate added as an additional regressor in the second stage) was not statistically significant in the second stage logistic model, which suggested that the treatment selection model (first stage model) had been fully adjusted for selection bias by the explanatory variables included in the model. Using this model, the unknown or unobserved confounding factors had little or no effect on assigning patients to different study groups.

Discussion

Early studies of antibiotic prophylaxis often failed to show efficacy due to the fact that antibiotics were started after surgery had been completed.[13] The seminal study to investigate the relationship between the appropriate timing of antibiotic prophylaxis and surgical wound infections was performed by Classen *et al.*[9] In this study, 2847 patients undergoing clean or clean-contaminated surgery were prospectively monitored for the timing of antibiotic prophylaxis and the incidence of SSI. The study demonstrated

Table 3. Sensitivity analysis results

Time of vancomycin administration	Odds ratio from original analysis (95% CI)	Odds ratio from two-stage Heckman model (95% CI)
0–15 min	11.6 (2.6–52.4)	10.7 (5.1–22.5)
16–60 min	1	1
61–120 min	2.3 (0.98–5.61)	2.2 (1.4–2.3)
121–180 min	2.6 (1.1–6.2)	2.3 (1.5–3.5)
>180 min	2.1 (0.82–5.62)	1.9 (1.2–3.1)

that the administration of antibiotics during the 2 h before the surgical incision was associated with the lowest incidence of SSI compared with administration of antibiotics post-operatively or at earlier time periods before the surgical incision. Galandiuk *et al*.[8] combined the results of two prospective randomized trials of 221 patients undergoing surgery of the gastrointestinal tract and investigated the role of antibiotic prophylaxis timing. In this study, administration of antibiotics within 16–60 min was associated with the lowest rates of infectious complications. Both of these studies used β-lactam antibiotics, either cephalosporins or piperacillin, for surgical prophylaxis. Based on these and other studies, current recommendations for the appropriate timing of antibiotic prophylaxis state that the infusion of the first antimicrobial dose should begin within 60 min before incision.[2] Due to increased rates of SSI caused by methicillin-resistant *Staphylococcus* species, many institutions have begun to use vancomycin for surgical prophylaxis.[14] It should be noted that vancomycin is not recommended for institutions without prohibitively high rates of methicillin-resistant *Staphylococcus* species as several studies have shown equivalent or superior outcomes with β-lactam antibiotics compared with vancomycin for surgical prophylaxis and the increased risk of VRE colonization.[5,15–17] Due to a requirement for a longer infusion time of at least 1 h, it is recommended that vancomycin should be given within 120 min before the incision. However, the relation between the timing of vancomycin administration in clinical practice and post-operative SSI has never been studied. Due to the long half-life of vancomycin, it was hypothesized before this study began that it was possible that the timing recommendation may be lengthened beyond the suggested 120 min before incision.

In the current study of 2048 patients undergoing CABG or valve replacement cardiac surgery, a clear pattern of infection risk and timing of vancomycin prophylaxis was apparent. Patients given vancomycin from 0 to 15 min before the first surgical incisions had 11.6 times increased odds of SSI compared with patients given vancomycin 16–60 min before the first surgical incision. After this time, patients given vancomycin more than 60 min before the first surgical incision had approximately two times increased odds of surgical site infection compared with patients given vancomycin 16–60 min before the first surgical incisions. In the Galandiuk study described above, it was thought that incomplete infusion of antibiotic prophylaxis was responsible for the high infection rates observed in the 0–15 min group. This is unlikely the case in the current study as all patients given vancomycin within 60 min before the first surgical incision finished the infusion after the start of surgery. Potentially, the decreased efficacy observed in the early time period in this study was caused by inadequate penetration of the drug to the surgical site. Vancomycin penetration into heart and mediastinal tissues was assessed in 10 patients given vancomycin immediately before anesthesia.[18] Vancomycin concentrations above the MIC for *S. aureus* (MIC = 1 mg/L) or *S. epidermidis* (MIC = 2 mg/L) were achieved in 67–88% of tissue samples obtained at the beginning of surgery. A rapid increase in the volume of distribution of vancomycin, which corresponds to decreased plasma and surgical site concentrations, has also been described at the initiation of cardiopulmonary bypass.[19] These alterations in the pharmacokinetics of vancomycin may be exacerbated in patients with decreased circulation to the surgical site such as diabetic patients or patients with atherosclerosis, further augmenting the risk of infection if surgery is started within 15 min of the vancomycin infusion.

Why the decreased efficacy of vancomycin was observed after 1 h will require further study. The importance of optimizing antibiotic prophylaxis infusion times was first demonstrated using a guinea pig model of subcutaneous *S. aureus* infection.[20] Administration of penicillin before or within the first hour after inoculation reduced the size of the experimentally infected surgical sites. Each delay of an hour in antibiotic administration increased the size of infected tissue involvement until the third hour, at which time the lesion approached the size of the untreated animals. In cardiac surgery, a small case–control study of 201 patients of whom 5% received vancomycin demonstrated that the administration of antibiotic prophylaxis within 60 min of the surgical incision decreased the risk of deep SSI.[21] Why this increased efficacy is observed during this early time period will require further study. It is possible that concentrations well above the expected MIC of the organism are required for optimal antibiotic efficacy. This is supported by a rat model of staphylococcal infection after haemorrhagic shock.[22] Rats were given increased doses of the antibiotic. Antibiotics concentrations of six times the *S. aureus* MIC were required in this model to prevent development of bacterial abscesses.

Strengths of the present study include a large sample size, prospective study design, multivariate logistic regression techniques to control known confounders and a robust sensitivity analysis. Patients were not screened for *S. aureus* colonization prior to surgery and thus we were unable to evaluate this risk factor in our model. The allocation of vancomycin timing group was not randomized and it is possible that differences in baseline characteristics exist among study groups due to selection bias; however, the results of a Heckman two-stage model suggested that this sample selection bias had been well controlled by the covariates included in the logistic regression model. Randomized controlled trials in this area would require extremely large sample sizes and would be constrained by costs, logistical difficulties and ethical obligations to provide patients with optimal therapy. Likewise, although more than 2000 patients were studied, the study lacked statistical power to stratify SSI as superficial, deep or organ-space infection due to the relative scarcity of SSI overall. We did not assess the effect of renal dysfunction on appropriate vancomycin timing and this will need to be explored in the future. At St Luke's Episcopal Hospital, when the decision was made to change to vancomycin for surgical prophylaxis, our antibiotic infusion protocol was changed to give more time to allow the antibiotic to be completely infused. Thus, the majority of our patients started their infusion within 60–120 min of the start time of surgery. Based on the results of the present study, vancomycin infusion must be started more than 15 min before the start of surgery, optimally between 16 and 60 min before the first surgical incision.

Conclusions

In patients undergoing CABG or valve replacement surgery, the administration of vancomycin prophylaxis within 16–60 min before the first surgical incision reduced the risk of SSI.

Acknowledgements

This paper was presented at an oral symposium of the Forty-fifth Interscience Conference on Antimicrobial Agents and

Chemotherapy (ICAAC), Washington, DC, 2005. The study was funded by an internal grant at St Luke's Episcopal Hospital, Houston, TX, USA.

Transparency declarations

Potential conflict of interest: K. W. G. has received past research support from Merck & Co., Inc. and is on the speaker's bureau for Ortho McNeil Pharmaceuticals. The remaining authors have none to declare.

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