Direct Oral Anticoagulants in Patients With VTE and Cancer

A Systematic Review and Meta-analysis

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BACKGROUND: Direct oral anticoagulants (DOAs) have been shown to be as effective and at least as safe as conventional anticoagulation for the prevention of recurrences in patients with VTE. Whether this is the case in patients with cancer-associated VTE remains undefined.

METHODS: We performed a meta-analysis of randomized controlled trials with the aim of assessing the efficacy and safety of DOAs in patients with VTE and cancer. MEDLINE, EMBASE, and CENTRAL were searched up to December 2013 with no language restriction. The primary outcome of the analysis was recurrent VTE. Data on major bleeding (MB) and clinically relevant nonmajor bleeding were analyzed. Data were pooled and compared by ORs and 95% CIs.

RESULTS: Overall, 10 studies comparing DOAs with conventional anticoagulation for treatment of VTE including patients with cancer were included in the review. Six studies were included in the meta-analysis (two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban), accounting for a total of 1,132 patients. VTE recurred in 23 of 595 (3.9%) and in 32 of 537 (6.0%) patients with cancer treated with DOAs and conventional treatment, respectively (OR, 0.63; 95% CI, 0.37-1.10; *I*², 0%). MB occurred in 3.2% and 4.2% of patients receiving DOAs and conventional treatment, respectively (OR, 0.77; 95% CI, 0.41-1.44; *I*², 0%).

CONCLUSIONS: DOAs seem to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer. Further clinical trials in patients with cancer-associated VTE should be performed to confirm these results. CHEST 2015; 147(2):475-483

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ABBREVIATIONS: CLOT = Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients With Venous Thromboembolism; DOA = direct oral anticoagulant; LMWH = low-molecular-weight heparin; RCT = randomized clinical trial; TTR = time in therapeutic range

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Patients with malignancy have a fourfold to sevenfold greater risk of VTE when compared with patients without cancer.^{1,2} The risk for recurrent VTE while on anticoagulant treatment is particularly high in patients with cancer, as it is the cause of bleeding complications.³⁻⁵ Low-molecular-weight heparins (LMWHs) have been shown to be more effective than and as safe as conventional anticoagulation with initial LMWH followed by vitamin K antagonists.⁶⁻⁹ Thus, LMWHs are currently recommended over anticoagulation with vitamin K antagonists for the treatment of VTE in patients with cancer.¹⁰

A risk for recurrence as high as 15% per year once anticoagulation treatment is withdrawn¹⁰ candidate patients with cancer-associated VTE to indefinite anticoagulation treatment. Thus, extended anticoagulant therapy beyond 3 months (and until cancer is cured) is recommended in these patients; extended treatment is suggested even in case of high bleeding risk.¹⁰ Consistent recommendations have been released by the different guidelines.¹¹⁻¹⁴ Practical issues regarding the long-term use of LMWH include the cost of the drug, the feasibility of longterm parenteral therapy, quality of life, and also the lack of evidence of their efficacy and safety when given indefinitely.

New direct anti-Xa and anti-IIa oral anticoagulants with no recommended need for laboratory monitoring or dose adjustment have been shown in trials to be as effective as and probably safer than conventional anticoagulation for the treatment of VTE.¹⁵⁻²¹ Their predictable response, oral administration, and fixed-dose regimens make direct oral anticoagulants (DOAs) attractive for the treatment of VTE in patients with cancer. However, only a minor proportion of patients with cancer (about 5%) was included in each of these trials. Thus, whether the results of phase 3 trials also apply to the general population of patients with cancer remains undefined. We performed a systematic review and a meta-analysis to assess the efficacy and safety of DOAs in patients with VTE and cancer.

Materials and Methods

Data Sources and Searches

A protocol for this review was prospectively developed detailing the specific objectives; criteria for study selection; approach to assess study quality, outcomes, and statistical methods. We performed an unrestricted search in MEDLINE, EMBASE, and CENTRAL through December 17, 2013. The search strategy is reported in e-Table 1. No language restrictions were applied. Reference lists of retrieved articles and review articles were manually searched for other relevant studies. The term ximelagatran was excluded from the search because this drug was withdrawn from clinical use.

Study Selection

Two reviewers (M. C. V. and F. G.) performed study selection independently, with disagreements resolved through discussion and the opinion of a third reviewer (C. B.). Studies were considered potentially eligible for this systematic review if they met the following predetermined criteria: (1) they were phase 3 randomized clinical trials (RCTs) or phase 2 RCTs; (2) DOAs were compared with therapeutic doses of vitamin K antagonists in patients with VTE; (3) patients defined as having "active cancer" were included; and (4) VTE recurrences and bleeding events were objectively assessed in both groups. Phase 2 RCTs were eligible for inclusion if at least one of the evaluated dosages was subsequently used in phase 3 trials. Studies could be included in the meta-analysis if the following data were available: number of patients with and without study outcomes (VTE recurrences and bleedings) among patients with cancer receiving DOAs and among those receiving conventional treatment (heparin followed by vitamin K antagonists). For duplicate publications, the most complete was considered. To assess agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance.22

Data Extraction and Quality Assessment

Data were extracted and presented according to the Providing Innovative Service Models and Assessment (PRISMA) criteria.²³ For each study, the following data were extracted independently by two authors (M. C. V. and F. G.): general data (study design, year of publication), population characteristics (number, mean age, sex), and treatment (therapeutic indication, type of drug, dose, duration). Information on the following outcomes was collected for the two treatment groups where available: number of VTE recurrences, mortality, and major and clinically relevant nonmajor bleedings. Outcomes were reported as defined in the individual studies.

Study quality was assessed by two reviewers (M. C. V. and F. G.) using the Cochrane Collaboration's tool to assess risk of bias in randomized trials, which covers the following bias domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias.²⁴ High quality was defined when at least six of the seven criteria within these bias domains were satisfied. We resolved disagreements about study data extraction and quality assessment by consensus or by discussion with a third reviewer (C. B.).

Statistical Analysis

We determined pooled ORs and 95% CIs for VTE recurrences in patients with cancer who received heparin followed by vitamin K antagonists or treatment with a DOA. Furthermore, the pooled ORs of VTE recurrence and major or clinically relevant nonmajor bleeding (clinically relevant bleeding) in the two treatment arms were calculated.

Data were pooled by using the Mantel-Haenszel method²⁵; we reported results according to a fixed-effects model in the absence of significant heterogeneity and to a random-effects model in the presence of significant heterogeneity.²⁶ We used the random effects model because it accounts for variations between studies in addition to sampling error within studies. The appropriateness of pooling data across studies was assessed using the Cochran χ^2 test and the I^2 test for heterogeneity, which measure the inconsistency across the study results and describe the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error:^{26,27} Statistically significant heterogeneity was considered to be present when P < .10 and $I^2 > 50\%$. Funnel plots were used to assess for publication bias.²⁵

We planned to perform separate analyses of study period (6 months and 12 months), studies including study drug (new anti-Xa and anti-IIa), and study drug approach with DOAs (ie, a single drug and heparin/DOA). A meta-regression analysis was performed with the following variables: mean value of time in therapeutic range (TTR) and mean follow-up duration. Both data were derived from the overall study population. The statistical analyses, forest plots, and publication bias analyses were produced with Review Manager release 5.1 (The Cochrane Collaboration) and STATA/SE 12 (StataCorp LP).

Results

Overall, 915 studies were found, and 26 were selected as potentially relevant. The flow diagram for study selection is reported in Figure 1. Ten studies that reported data on patients with cancer were included in the systematic review. Interobserver agreement for study selection was good ($\kappa = 0.87$).

Baseline characteristics of the studies included in the systematic review are reported in Table 1. All trials were randomized. Reports on three phase 2 trials were selected (one on apixaban²⁸ and two on rivaroxaban^{29,30}) and on seven phase 3 trials (one on apixaban,²¹ three on dabigatran,¹⁸⁻²⁰ one on edoxaban,¹⁶ and two on rivaroxaban^{15,17}). Study size ranged from 520 to 8,240 patients and the rates of included patients with cancer ranged from 2.5% to 9.4%.

All the phase 3 trials showed similar rates of VTE recurrence with respect to the comparator (heparin/vitamin K antagonists), and noninferiority was achieved for all these trials. The rates of major and clinically relevant nonmajor bleeding are shown in Table 1.

Meta-analysis

Ten studies were considered for the meta-analysis: Data from two phase 2 trials, including a DOA regimen subsequently used in phase 3 trials,^{28,29} were not available; one study reporting on the extended treatment of VTE was excluded²⁰; and one phase 2 study³⁰ was excluded because it reported on a regimen not used in the phase 3 trial. Overall, six studies reported separate data on VTE recurrences and bleeding events in patients with cancer, and were included in the meta-analysis.

Data on patients with cancer from the two trials with dabigatran^{18,19} are reported as they are shown in the pooled analyses.^{19,31} Data on patients with cancer from the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line



Figure 1 – Flow diagram for study selection. NOAC = new oral anticoagulant.

TABLE 1] Baseline Characteristics of the Studies Included in the Systematic Rev	/iew
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Study	Year	Study Design	Study Phase	Study Drug	Dose	Comparator	Study Period	Randomized Patients, No.	Patients With Active Cancer, No. (%)	TTR, %	Overall Death, Study Drug vs Comparator, %	Recurrent VTE or VTE-Related Death, Study Drug vs Comparator, %	CRB, Study Drug vs Comparator, %	Included in the Meta- analysis
AMPLIFY ²¹	2013	DB	III	Apix.	10 mg bid for 7 d followed by 5 mg bid	Heparin/ VKA	6 mo	5,395	169 (3.1)	61	1.5 vs 1.9	2.3 vs 2.7	4.3 vs 9.7	Yes
BOTTICELLI ²⁸	2008	Open (DB for apix. doses)	II	Apix.	5 mg or 10 mg bid or 20 mg qd	Heparin/ VKA	84-91 d	520	37 (7.1)	57	2.3 or 0.7 or 0.8 vs 0	2.6 or 3.2 or 1.7 vs 2.5	8.6 or 4.5 or 8.9 vs 7.9	No
EINSTEIN-DVT ¹⁵	2010	Open	III	Riv.	15 mg bid for 3 wk followed by 20 mg qd	Heparin/ VKA	12 moª	3,449	207 (6.0)	57.7	2.2 vs 2.9	2.1 vs 3.0	8.1 vs 8.1	Yes
EINSTEIN-DVT Dose- Ranging ²⁹	2008	Open (DB for riv. doses)	II	Riv.	20 mg or 30 mg or 40 mg qd	Heparin/ VKA	3 mo⊳	543	51 (9.4)	50.3	3.0 or 6.0 or 1.5 vs 3.6	2.6 or 3.6 or 1.7 vs 6.9	5.9 or 6.0 or 2.2 vs 8.8	No
EINSTEIN-PE ¹⁷	2012	Open	III	Riv.	15 mg bid for 3 wk followed by 20 mg qd	Heparin/ VKA	12 moª	4,832	223 (4.6)	62.7	2.4 vs 2.1	2.1 vs 1.8	10.3 vs 11.4	Yes
HOKUSAI ¹⁶	2013	DB	III	Heparin/ Edox.	60 mg once daily or 30 mg once daily	Heparin/ VKA	12 mo ^c	8,240	208 (2.5)	63.5	3.2 vs 3.1	3.2 vs 3.5	8.5 vs 10.3	Yes
ODIXa-DVT ³⁰	2007	Open (DB for riv. doses)	II	Riv.	10 or 20 or 30 mg bid or 40 mg qd	Heparin/ VKA	12 wk	528	16 (3.0)	60	2.7 (riv.) vs 0.8	1.9 or 2.0 or 1.8 or 2.6 vs 0.9	5.0 or 9.4 or 10.7 or 11.6 vs 6.3 (any bleeding)	No

(Continued)

											Overall Death.	Recurrent VTE or	CKB	
									Patients		Study	VTE-Related	Study	Included
									With Active		Drug vs	Death, Study	Drug vs	in the
		Study	Study	Study			Study	Randomized	Cancer,		Comparator,	Drug vs	Comparator,	Meta-
Study	Year	Design	Phase	Drug	Dose	Comparator	Period	Patients, No.	No. (%)	TTR, %	%	Comparator, %	%	analysis
RE-COVER ¹⁸	2009	DB	II	Heparin/	150 mg bid	Heparin/	6 mo	2,539	121 (4.8)	60	1.6	2.7	5.6	Yes
				Dab.		VKA					vs 1.7	vs 2.5	vs 8.8	
RE-COVER II ¹⁹	2013	DB	III	Heparin/	150 mg bid	Heparin/	6 mo	2,589	100 (3.9)	57	2.0	2.3	5.0	Yes
				Dab.		VKA					vs 1.9	vs 2.2	vs 7.9	
RE-MEDY ²⁰	2013	DB	III	Dab.	150 mg bid	Heparin/	6-36 mo	2,856	119 (4.2)	65.3	1.2	1.8	5.6	No
						VKA					vs 1.3	vs 1.3	vs 10.2	
apix. = apixaban; CRE /KA = vitamin K antac	3 = majo	or clinically n	elevant	nonmajor blee	ding; dab. = dabigat	tran; DB = doub	le blind; edox	. = edoxaban; u	qd = each day;	; riv. = riv	/aroxaban; TTR	= time in thera	peutic range;	
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Therapy (AMPLIFY) study²¹ have been provided by the AMPLIFY steering committee and reported as presented at the European Society of Cardiology Congress 2014.³² Quality assessment items are summarized in e-Table 2.

VTE Recurrence

VTE recurrence was evaluated in six studies (two with dabigatran,^{18,19} two with rivaroxaban,^{15,17} one with edoxaban,¹⁶ and one with apixaban²¹) and occurred in 23 of 595 patients (3.9%) treated with DOAs and in 32 of 537 patients (6.0%) treated with comparator. DOAs were associated with a nonsignificant reduction in VTE recurrence (OR, 0.63; 95% CI, 0.37-1.10; *I*², 0%) (Fig 2). Funnel plot inspection did not reveal publication bias (e-Fig 1).

Bleeding Events

Major bleeding was evaluated in six studies and occurred in 19 of 587 patients (3.2%) treated with DOAs and in 22 of 527 patients (4.2%) treated with the comparator.^{15-17,19,21,31,33,34} DOAs were associated with a nonsignificant reduction in major bleeding (OR, 0.77; 95% CI, 0.41-1.44; *I*², 0%) (Fig 3A). Funnel plot inspection did not reveal publication bias (e-Fig 2).

Clinically relevant bleeding was evaluated in six studies and occurred in 85 of 587 patients (14.5%) treated with DOAs and in 87 of 527 patients (16.5%) treated with the comparator.^{15-17,21,31} A nonsignificant reduction in clinically relevant bleeding was shown with the use of DOAs (OR, 0.85; 95% CI, 0.62-1.18; *I*², 1% (Fig 3B). Funnel plot inspection did not reveal publication bias (e-Fig 3).

Sensitivity Analysis

Sensitivity analysis including only high-quality studies confirmed the results of the efficacy and safety analyses in all the selected trials (e-Figs 4-7).

Subgroup Analyses

Treatment duration: 3 mo, 6 mo, or 12 mo.

duration: 85 d. duration: 3 mo to 6 mo.

Treatment Treatment A subgroup analysis on studies comparing new anti-Xa^{15-17,21} or anti-IIa¹⁹ drugs with the comparator was performed. The OR for recurrent VTE in the group receiving anti-Xa drugs (four studies, 797 patients) was 0.56 (95% CI, 0.27-1.14) and was 0.77 (95% CI, 0.32-1.83) in the group receiving anti-IIa drugs (two studies, 335 patients) (e-Figs 8, 9).

An analysis on studies reporting on a single-drug approach with DOAs vs the use of heparin before DOA administration was also performed. Three studies (589 patients) were included in the analysis on the

TABLE 1] (continued)

	DOA Comparator				Odds Ratio	Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fi	xed, 95% C	:	
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]					
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]					
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]					
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]			<u> </u>		
RECOVER & 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]			∎┼─		
Total (95% Cl)		595		537	100.0%	0.63 [0.37, 1.10]					
Total events	23		32								
Heterogeneity: Chi ² = 0.3	36, df = 4	(P = 0.9	99); l² = 09	%						10	
Test for overall effect: Z	= 1.62 (P	= 0.10))				0.01	U.I Favors DO	A Favors c	ompara	ator

Figure 2 – Use of DOA and VTE recurrence in patients with cancer. df = degrees of freedom; DOA = direct oral anticoagulant; M-H = Mantel-Haenszel method.

single-drug approach^{15,17,21} and three studies (429 patients) reported on the heparin/DOA approach.^{16,19} In studies reporting on the single-drug approach, recurrent VTE occurred in 2.8% of patients receiving DOAs and 4.7% of patients receiving comparator (OR, 0.59; 95% CI, 0.25-1.40). In studies reporting on heparin/DOA, recurrent VTE occurred in 3.6% of patients receiving heparin/DOA and in 5.8% of patients receiving comparator (OR, 0.60; 95% CI, 0.24-1.50) (e-Figs 10, 11).

Meta-regression analyses showed no association of mean TTR values (P = .696) or mean follow-up duration (P = .819) with the effect size.

When patients from the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis (EINSTEIN) studies,³⁴ who were diagnosed with cancer during the studies, were included in the analyses, the results concerning efficacy (1,299 patients; OR, 0.67; 95% CI, 0.39-1.08; *I*², 0%) and major bleeding (1,283 patients; OR, 0.71; 95% CI, 0.40-1.25; *I*², 0%) were confirmed.

Discussion

This study shows that the efficacy and safety profile of new anti-Xa and anti-IIa drugs for VTE treatment in patients with cancer is similar to that observed in



Figure 3 – *A*, Use of DOA and major bleeding in patients with cancer. *B*, Use of DOA and clinically relevant bleeding in patients with cancer. See Figure 2 legend for expansion of abbreviations.

patients without cancer. A favorable trend toward reduction of recurrent VTE was observed without concern in terms of clinically relevant bleedings.

We found a nonsignificant reduction of recurrent VTE of about 40% in favor of DOAs compared with conventional treatment with heparin followed by vitamin K antagonists. The reduction was consistent across all the included studies. Of note, the observed risk reduction in the patients with and without cancer overall is about 10%.

LMWHs are currently recommended for the treatment of VTE in patients with cancer. No clinical trial is currently available comparing LMWHs with new oral anticoagulants in patients with cancer.

A risk reduction of about 50% was observed with dalteparin compared with conventional anticoagulation in 672 patients with cancer included in the randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer (CLOT) study.6 However, particularly high rates of recurrent VTE were observed in this study (about 8% and 16% in patients randomized to dalteparin or conventional anticoagulation, respectively). The improved level of anticoagulation over time obtained with conventional anticoagulation (heparin/vitamin K antagonists) in phase 3 trials with DOAs compared with that of the CLOT study (time in the range of about 60% compared with 46%, respectively) could explain the lower recurrence rate observed with these agents (Table 1). On the other hand, it is possible that patients with advanced cancer that qualified for inclusion in the CLOT study were excluded from phase 3 trials with DOAs. These patients are known to have a particularly high risk for recurrent VTE. A Cochrane systematic review and metaanalysis on the efficacy and safety of LMWH and oral anticoagulants for the long-term treatment of VTE in patients with cancer was published in 2011.35 LMWH compared with a vitamin K antagonist was shown to significantly reduce recurrences of VTE (1,018 patients; hazard ratio, 0.47; 95% CI, 0.32-0.71). An analysis was also reported for dabigatran only, including the results of the Efficacy and Safety of Dabigatran Compared to Warfarin for 6-Month Treatment of Acute Symptomatic Venous Thromboembolism (RECOVER) I study.

Our analysis shows that new anti-Xa and anti-IIa drugs are probably as safe as heparin followed by vitamin K antagonists for the treatment of VTE in patients with cancer. Of note, the observed risk reduction in patients with and without cancer is about 30% for both major bleeding and for clinically relevant bleeding in patients receiving DOAs, with respect to heparin followed by vitamin K antagonists.

Results from studies with different agents have been combined in this meta-analysis, but the analysis is not powered to show differences among individual agents. However, there were no signs of heterogeneity when the outcomes of recurrent VTE or clinically relevant bleeding were analyzed, thus suggesting that the results, in terms of efficacy and safety, are consistent across all the new agents included in our study. Pooled results from the EINSTEIN trials on DVT and on pulmonary embolism, as well as from the RECOVER I and II trials, showed a trend toward reduction in primary efficacy outcome in favor of both the anti-Xa and the anti-IIa drugs (2.6% vs 4.0% and 3.5% vs 4.7%, respectively) in patients with cancer.^{19,34}

For their fixed-dose regimens and oral administration, DOAs are clinically attractive drugs for the treatment of VTE in patients with cancer. This is mainly due to the improved feasibility of long-term treatment. However, some disadvantages could derive from unknown interactions between these agents and anticancer ther apies as well as from chemotherapy-related vomiting. Moreover, potential interactions between DOAs and azole-antimycotic agents, commonly used in patients on chemotherapy, should be considered. In this view, our results should be considered as hypothesis generating and further ad hoc clinical trials with individual DOAs should be conducted to confirm their efficacy and safety in this setting.

Our study has some limitations in addition to those intrinsic to the meta-analysis approach, which combines heterogeneous datasets. As an aggregated data metaanalysis based on study subgroups, we could not adjust for TTR, for type of VTE, and type and stage of cancer. Meta-regression analyses were performed applying to patients with cancer mean TTRs and mean follow-up duration of the overall study populations, as separate data on patients with cancer were not available. The rationale for these analyses was the assumption that those values found in the overall study populations could apply to the subpopulations of patients with cancer. The term "active cancer," which is used across all the studies, is not better defined in the study protocols of the individual studies. Patients with cancer for whom treatment with LMWH was considered more appropriate were not included in some of the studies. Thus, it is debatable

whether patients with cancer included in the analyzed clinical trials are representative of patients with cancer overall. Moreover, the small percentage of patients with cancer included in the studies (Table 1) did not allow us to reach an adequate sample and a more precise estimation of pooled effect sizes. In fact, to demonstrate a reduction in VTE recurrence from 5% to 3%, at least 1,500 patients should have been analyzed. Last, LMWH is the most common anticoagulant used for the treatment of VTE in patients with cancer. So the comparator of this meta-analysis is not the usual medical treatment; in many countries, vitamin K antagonists are still used in patients with cancer and VTE.

Conclusions

New anti-Xa and anti-IIa drugs seem to be at least as effective and safe as conventional anticoagulant treatment with vitamin K antagonists for prevention of VTE recurrence in cancer patients. Ad hoc clinical trials should be conducted to confirm our results.

Acknowledgments

Author contributions: M. C. V. served as principal author, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. M. C. V., F. G., and C. B. contributed to the study concept and design and data analysis; M. C. V., F. G., G. A., and C. B. contributed to data acquisition and interpretation; M. C. V. and F. G. contributed to drafting of the manuscript; and G. A. and C. B. contributed to revision of the manuscript.

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Additional information: The e-Tables and e-Figures can be found in the Supplemental Materials section of the online article.

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