Effect of antifibrinolytic therapy with tranexamic acid on abdominal aortic aneurysm shrinkage after endovascular repair

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Objective: **The long-term outcomes of endovascular abdominal aortic aneurysm repair (EVAR) remain to be determined, but patients with aneurysm shrinkage after EVAR appear to have a good prognosis. We previously observed that antiplatelet therapy is a risk factor for lack of aneurysm shrinkage, a finding suggesting that coagulation and fibrinolysis play roles in shrinkage. We therefore studied the effect of antifibrinolytic therapy with tranexamic acid (TXA) on aneurysm shrinkage after EVAR.**
Methods: **From May 2007 to May 2012, EVAR was performed in 187 patients, 165 of whom had an enhanced computed tomographic evaluation 6 months after their procedure. Six of the 165 patients were excluded from the study because they had a type Ia endoleak or coil embolization to treat a type II endoleak ≤6 months after EVAR. Of the remaining 159 patients, 110 underwent EVAR before we started to use TXA in our centers. TXA therapy (1500 mg/d for 6 months) began in January 2011, and 48 patients completed the treatment regimen. Patients not treated with TXA were compared with those given TXA. Analyses to identify risk factors for lack of aneurysm shrinkage were performed.**
Results: **No patient had a thromboembolic event. There were no significant differences between the no-TXA and TXA groups in demographics, aneurysm characteristics, prosthesis implanted, type II endoleak occurrence during EVAR or 1 or 6 months afterward, or aneurysm shrinkage at 1 month. However, at 6 months after EVAR, the TXA group had significantly greater aneurysm shrinkage ($P = .035$) and a significantly higher percentage of patients with >4 mm in shrinkage ($P = .010$). Multiple regression analysis showed aneurysm diameter, type II endoleak 6 months after EVAR, and TXA treatment were independently associated with aneurysm shrinkage or lack of shrinkage.**
Conclusions: **Antifibrinolytic therapy with TXA was associated with aneurysm shrinkage after EVAR. Studies to identify the dosage of TXA that is optimally safe and effective in this application, as well as investigations of the best timing and route (parenteral vs oral) for TXA administration, are warranted. (J Vasc Surg 2014;59:1203-8.)**

Endovascular abdominal aortic aneurysm (AAA) repair (EVAR) is widely and increasingly used because it has a lower operative mortality rate than surgical AAA repair and favorable short-term results. However, some randomized studies found that, over the long term (4 to 6 years), patients who underwent EVAR had a survival rate similar to or lower than that of patients given open repair as well as significantly higher rates of reinterventions and graft-related complications.[1,2] Expansion of the aneurysm sac after AAA repair has been reported to be a risk factor for rupture,[3] and shrinkage of the sac is considered to indicate successful exclusion of the AAA from the circulation and to be a strong predictor of good long-term results.[4,5]

We previously found that multiagent antiplatelet therapy was associated with a lack of aneurysm shrinkage after EVAR.[6] This finding suggests that a balance between coagulation and fibrinolysis plays a role in post-EVAR aneurysm shrinkage and that administration of an antifibrinolytic agent might promote shrinkage.

Tranexamic acid (TXA) is a synthetic lysine analog that binds reversibly to plasminogen, thereby blocking plasminogen activation and transformation to plasmin. Because plasmin is responsible for the degradation of fibrin, a protein that forms the framework of blood clots, TXA exerts its antifibrinolytic effect by inhibiting fibrin degradation. We therefore conducted a study to determine whether administration of TXA affected aneurysm shrinkage in patients who had undergone EVAR.

METHODS

This study was a retrospective review of the medical records of patients who underwent EVAR from May 2007 to May 2012 at five institutions. The study protocol, including the administration of TXA, was approved by the

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Ethics Committee at each center, and all patients provided informed consent to their participation. Of the 187 patients identified as having undergone EVAR during the study period, the study initially enrolled only the 165 who had an enhanced computerized tomographic evaluation 6 months after the procedure. The study subsequently excluded four patients who had a type Ia endoleak and two who underwent transarterial coil embolization for a type II endoleak ≤6 months of EVAR. Of the remaining patients, 110 had undergone EVAR before we began to administer TXA after the procedure (ie, before the end of 2011).

Beginning in January 2011, patients who underwent EVAR at our institutions received TXA (1500 mg/d orally) from the morning after EVAR until 6 months afterward. All patients returned for an outpatient visit at our hospitals every 4 to 8 weeks during those 6 months, and their compliance with TXA therapy was assessed at each visit. Forty-eight patients completed the entire TXA treatment regimen. TXA therapy was discontinued in another patient because of development of deep vein thrombosis 3 months after EVAR, even though it could not be determined whether TXA had caused the problem. This patient was excluded from further analysis.

Patient demographics, concomitant diseases, aneurysm characteristics, endovascular device implanted, operating time, and postoperative antiplatelet and anticoagulation therapy in patients in the TXA and no-TXA groups were compared by using the nonpaired *t*-test and χ^2 test. Multiagent antiplatelet therapy was defined as treatment with aspirin and clopidogrel bisulfate, ticlopidine hydrochloride, or cilostazol. In our institutions, antiplatelet therapy or anticoagulation therapy using warfarin is not stopped before EVAR.

Data from the 158 patients in the study were entered into a univariant analysis of factors possibly associated with aneurysm shrinkage at 1 and 6 months after EVAR. The univariant analysis used the nonpaired *t*-test, χ^2 test, and regression analysis. Variables found by this analysis to be associated with aneurysm shrinkage with a P value of $<.10$ were evaluated for a possible relationship with shrinkage in a multivariant assessment using multiple regression analysis. The effect of TXA therapy on aneurysm shrinkage in patients without and with a type II endoleak 6 months after EVAR and in patients not receiving and receiving multiagent antiplatelet therapy was evaluated by using χ^2 testing. A P value of $<.05$ was considered to represent a significant correlation. All statistical analyses were done with StatView 4 software (SAS Institute, Cary, NC).

RESULTS

At baseline (before or during EVAR), patients who received TXA were similar to those not given TXA with respect to all assessed characteristics (Table I), except that they were somewhat more likely to have received antiplatelet therapy ($P = .097$) and their suprarenal angle tended to be larger ($P = .079$). Preoperatively, patients in the no-TXA group had a maximum aneurysm diameter of 39 to 80 mm, whereas the maximum diameter in the TXA group was 40 to 85 mm. The percentage of patients in each group with a large maximum aneurysm diameter was similar: 16% in the no-TXA group and 23% in the TXA group for aneurysms >59 mm ($P = .259$); 9% and 15%, respectively, for aneurysms >64 mm ($P = .306$); and 5% and 10%, respectively, for aneurysms >69 mm ($P = .163$). Deep vein thrombosis developed in one patient, although whether this was related to TXA therapy could not be determined. No other patient in either group had a thromboembolic event (eg, acute coronary syndrome or cerebral infarction) during the study period.

At 1 month after EVAR, the TXA and no-TXA groups had a similar amount of aneurysm shrinkage. At 6 months, however, patients given TXA had significantly greater shrinkage (6.0 ± 4.8 mm vs 4.3 ± 4.8 mm; $P = .035$). Moreover, a significantly higher percentage of TXA-treated patients than untreated patients had shrinkage of >4 mm (58% [n = 28] vs 36% [n = 40]; $P = .010$). No patient in either group had an aneurysm enlargement of >4 mm.

Table I. Baseline and operative characteristics of patients who were and were not treated with tranexamic acid (*TXA*) after endovascular abdominal aortic aneurysm repair (EVAR)

Variable[a]	*No TXA (n = 110)*	*TXA (n = 48)*	P
Patient characteristics			
Age, years	76.3 ± 8.2	76.2 ± 7.2	.933
Female gender	19 (17)	7 (15)	.675
Hypertension	80 (73)	39 (81)	.253
Hyperlipidemia	39 (35)	23 (48)	.140
Diabetes mellitus, type 1 or 2	19 (17)	7 (15)	.675
Current smoker	75 (68)	34 (71)	.740
Chronic obstructive pulmonary disease	18 (16)	11 (23)	.328
Antiplatelet therapy[b]	53 (48)	30 (63)	.097
Multiagent antiplatelet therapy	33 (30)	18 (38)	.354
Anticoagulation therapy, warfarin	8 (7)	7 (15)	.149
Aneurysm characteristics			
Proximal neck length, mm	27 ± 9	27 ± 10	.765
Suprarenal angle,°	21 ± 21	28 ± 24	.079
Proximal neck angle,°	42 ± 26	43 ± 29	.900
Maximum diameter, mm	51.4 ± 8.2	53.4 ± 10.5	.200
Type of prosthesis[c]			.184
Zenith	50 (45)	20 (41)	
Excluder	44 (40)	18 (38)	
Powerlink	16 (15)	8 (17)	
Endurant	0	2 (4)	
Operating time, min	129 ± 48	134 ± 39	.550

[a]Continuous data are presented as the mean ± standard deviation and categoric data as number (%).
[b]Including aspirin alone.
[c]The manufacturers are Zenith: Cook, Bloomington, Ind; Excluder: W. L. Gore and Associates, Flagstaff, Ariz; Powerlink: Endologix, Irvine, Calif; and Endurant: Medtronic, Minneapolis, Minn.

At 6 months after EVAR, type II endoleaks were observed in 27% of patients in the no-TXA group (n = 30) and in 38% in the TXA group (n = 18); the difference was not significant ($P = .259$). There was also no significant difference in type II endoleak occurrence between patients receiving (31.3% [15 of 48]) and not receiving (32.7% [36 of 110]) multiagent antiplatelet therapy ($P > .999$) or between patients receiving (33.3% [5 of 15]) and not receiving (30.1% [43 of 143]) anticoagulant therapy ($P = .774$).

The univariant analysis showed that the TXA therapy, the presence of a type II endoleak at 1 month or 6 months after EVAR, proximal neck length, and preoperative maximum aneurysm diameter were each significantly associated with aneurysm shrinkage (Table II). Moreover, antiplatelet therapy and multiagent antiplatelet therapy were each somewhat associated with aneurysm shrinkage 6 months after EVAR. The multivariant analysis of these factors found that a type II endoleak 6 months after EVAR, preoperative maximum aneurysm diameter, and TXA therapy were each significantly associated with aneurysm shrinkage or lack of shrinkage at 6 months after EVAR (Table III).

The assessment of the effect of TXA therapy on aneurysm shrinkage in patients without and with a type II endoleak 6 months after EVAR (Fig 1) found that among those without an endoleak, aneurysm shrinkage occurred in 80% (24 of 30) of patients given TXA and in 45% (36 of 80) not given TXA, with the difference being significant ($P = .0015$). Among patients with a type II endoleak, the percentage of those with aneurysm shrinkage was low in the no-TXA (13% [4 of 30]) and the TXA group (22% [4 of 18]), with no significant difference between groups.

The analysis of the effect of TXA on aneurysm shrinkage in patients not receiving and receiving multiagent antiplatelet therapy (Fig 2) showed that among those not given TXA, a significantly lower percentage of patients who were receiving (15% [5 of 38]) this antiplatelet regimen had aneurysm shrinkage compared with those not receiving (46% [35 of 87]) antiplatelet therapy ($P = .0025$). Among patients given TXA, multiagent antiplatelet therapy had no significant effect on aneurysm shrinkage, which occurred in 61% (11 of 29) of patients receiving antiplatelet agents and in 57% (17 of 47) not given those agents ($P > .999$).

DISCUSSION

The goal of EVAR is to prevent aneurysm rupture by completely excluding the aneurysm from the circulation. Aneurysm shrinkage has been reported to be a favorable long-term outcome of EVAR.[4,5] The presence of a high-pressure endoleak (type I or type III) is an important risk factor for a lack of aneurysm shrinkage and aneurysm rupture,[7-9] but whether a type II endoleak has similar effects remains unknown. We previously observed that patients with a type II endoleak alone (no type I or III) had an increased risk of a lack of aneurysm shrinkage after EVAR, although shrinkage did occur in some patients, perhaps because they had a different endoleak subtype.[6]

Table II. Results of univariant analysis of factors possibly associated with aneurysm shrinkage after endovascular abdominal aortic aneurysm repair (EVAR) in 158 patients

Variable	*No.*	*Results*[a]	P
Patient characteristics			
Age		y = 8.2 − 0.05x[b]	.361
Gender			.918
Female	26	4.9 ± 4.7	
Male	132	4.8 ± 4.9	
Hypertension			.371
Absent	39	4.2 ± 4.9	
Present	119	4.9 ± 4.9	
Hyperlipidemia			.187
Absent	96	5.2 ± 5.1	
Present	62	4.2 ± 4.4	
Diabetes mellitus (type 1 or 2)			.808
Absent	132	4.9 ± 4.7	
Present	26	5.0 ± 5.6	
Smoking status			.257
Nonsmoker	49	4.1 ± 4.3	
Current smoker	109	5.1 ± 5.1	
Chronic obstructive pulmonary disease			.529
Absent	129	4.7 ± 4.8	
Present	29	5.3 ± 5.3	
Antiplatelet therapy including aspirin alone			.082
Not receiving	75	5.5 ± 5.0	
Receiving	83	4.2 ± 4.7	
Aspirin-alone antiplatelet therapy			.877
Not receiving	126	4.8 ± 4.9	
Receiving	32	4.7 ± 4.8	
Multiagent antiplatelet therapy			.085
Not receiving	107	5.3 ± 4.9	
Receiving	51	6.7 ± 5.8	
Aneurysm characteristics			
Proximal neck length		y = 7.5 − 0.10x	.023
Suprarenal angle		y = 4.2 + 0.02x	.180
Proximal neck angle		y = 3.6 + 0.03x	.111
Maximum diameter		y = 5.1 + 0.19x	<.001
Type II endoleak			
On EVAR completion angiogram			.284
No	113	5.1 ± 5.1	
Yes	45	4.1 ± 4.3	
1 month after EVAR on enhanced CT			<.001
No	110	5.8 ± 5.0	
Yes	48	2.6 ± 3.6	
6 months after EVAR on enhanced CT			<.001
No	110	6.1 ± 5.0	
Yes	48	1.9 ± 3.1	
TXA therapy			.035
No	110	4.3 ± 4.8	
Yes	48	6.0 ± 4.8	

CT, Computed tomography; *TXA*, tranexamic acid.
[a]The plus-minus values are mean ± standard deviation millimeters of shrinkage.
[b]*y* represents aneurysm shrinkage (mm); *x* represents each factor.

We also found that multiagent antiplatelet therapy was independently associated with a lack of aneurysm shrinkage.

Table III. Results of multiple regression analysis of factors possibly associated with aneurysm shrinkage at 6 months after endovascular abdominal aortic aneurysm repair (*EVAR*) in 158 patients

Variable	*r*	*Error*	*t*	P
Antiplatelet therapy including aspirin	−0.065	0.904	−0.695	.488
Multiagent antiplatelet therapy	−0.090	0.857	−0.972	.332
Aneurysm proximal neck length	−0.086	0.039	−1.188	.237
Maximum aneurysm diameter	0.231	0.040	3.155	.002
Type II endoleak				
1 month after EVAR	−0.075	0.947	−0.835	.405
6 months after EVAR	−0.330	0.953	−3.654	<.001
TXA therapy	0.199	0.737	2.846	.005

TXA, Tranexamic acid.

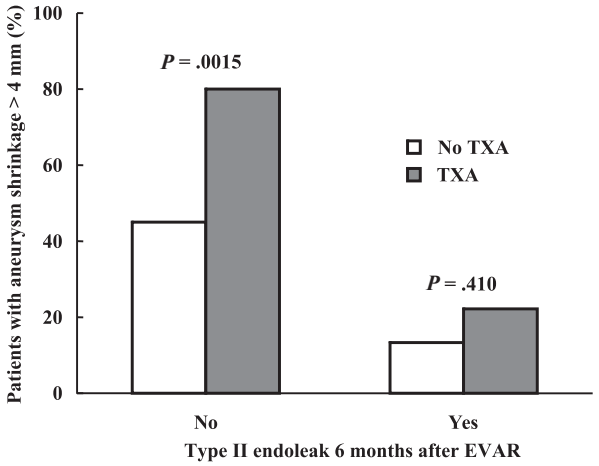

Fig 1. Percentage of patients with aneurysm shrinkage of >4 mm, according to whether they were treated with tranexamic acid (*TXA*) and had a type II endoleak 6 months after endovascular abdominal aortic aneurysm repair (*EVAR*).

Organization of a clot in the aneurysm sac that occludes the feeding artery is required to stop blood pressure transmission in an aneurysm.[10] After EVAR, clotting of the blood trapped between the stent graft and the aneurysm wall should occur. Engellau et al[11] used magnetic resonance imaging to assess the clot in the aneurysm sac after EVAR in 15 patients and detected an organized clot in two at 1 month after the procedure, in three of 12 patients at 6 months, and in four of 10 patients at 12 months; therefore, it appears that an organized clot does not develop in all patients who undergo EVAR. If the clot does not become organized, blood pressure associated with a type II endoleak or small artery not detectable by enhanced computed tomography would be transmitted to the aneurysm sac and the aneurysm would not shrink.

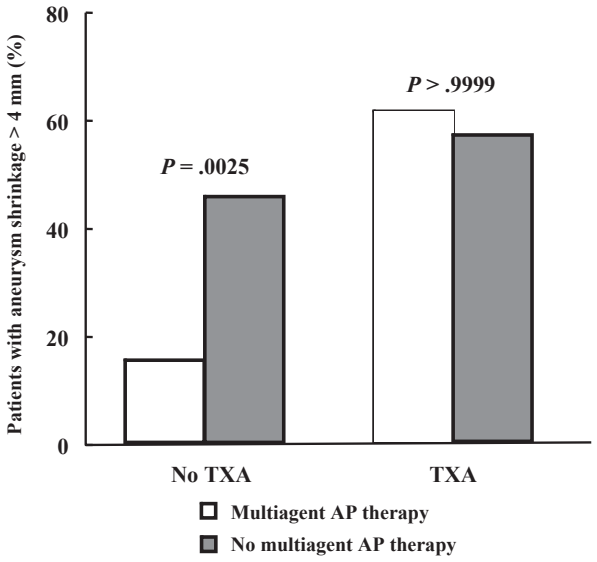

Fig 2. Percentage of patients with aneurysm shrinkage of >4 mm, according to whether they were treated with tranexamic acid (*TXA*) and with multiagent antiplatelet (*AP*) therapy after endovascular abdominal aortic aneurysm repair (EVAR).

In light of our previous findings, we hypothesized that multiagent antiplatelet therapy might be a risk factor for a lack of aneurysm shrinkage because it inhibits clot organization. In patients with aneurysm shrinkage despite the presence of a type II endoleak, blood pressure from the endoleak may not be transmitted to the aneurysm wall because of the presence of an organized clot in the aneurysm sac.

Whether a clot becomes organized depends on a balance between coagulation and fibrinolysis. The presence of an AAA, usually with mural thrombus, constitutes a prothrombotic diathesis.[12] In a study of changes in coagulation and fibrinolysis immediately after EVAR, Englberger et al[13] found that coagulation activity, with hyperfibrinolysis, increased on the first day after the procedure and subsided ≤5 days. Monaco et al[14] reported that platelet counts and levels of coagulation factors were decreased on the first, fifth, and 10th days after EVAR, whereas levels of D-dimer and fibrin degradation products were increased. Thus, consumption of coagulation factors as a result of clot formation in the aneurysm sac and hyperfibrinolysis appeared to occur acutely after EVAR and, according to Monaco et al,[14] lasted for ∼1 month. However, Aho et al[15] reported that levels of D-dimer, thrombin-antithrombin III complex, and prothrombin fragment 1 + 2 were high for 3 months after EVAR, and Bailey et al[16] found that they were high for 5 months. In a study of fibrinolytic activity for 12 months after EVAR, Abdelhamid et al[17] observed that fibrinolysis was increased for the first 6 months, as were levels of serum P-selectin, a marker of platelet activity. The findings of these studies indicate that prothrombotic diathesis, with hyperfibrinolysis, continues for several months after EVAR.

The relationship between aneurysm shrinkage and alterations in coagulation and fibrinolysis after EVAR was investigated by Serino et al,[18] who compared D-dimer levels in patients in whom the aneurysm had decreased in size (>6 months after EVAR) with levels in patients with an enlarged or unchanged aneurysm. They found that patients in the latter group had significantly higher levels. In a study by Conelissen et al[19] in 14 patients with an aneurysm that had not decreased by a mean of 2 years after EVAR, magnetic resonance imaging showed that the clot in the sac was not organized in half those patients.

On the basis of these findings, we speculated that AAAs might shrink after EVAR if clot organization in the aneurysm sac were promoted by activation of coagulation or inhibition of fibrinolysis. Activation of coagulation would not be practical, however, because it already occurs after EVAR. Furthermore, replenishment of platelets or coagulation factors by transfusing platelet-rich or fresh-frozen plasma might pose a risk of infection transmission. In contrast, suppression of fibrinolysis might be a feasible approach.

Several antifibrinolytic drugs have been evaluated over the years.[20,21] Aprotinin, a broad-spectrum serine protease inhibitor given intravenously, was withdrawn from the market in 2008 because of an increase in mortality among high-risk patients undergoing cardiac surgery.[20] Administration of ε-aminocaproic acid, a synthetic lysine analog, has been associated with onset of hypotension, cardiac arrhythmias, myopathy, and rhabdomyolysis.[20] TXA, another synthetic lysine analog, prevents the degeneration of fibrin[21] and has been used safely for several decades, primarily to mitigate the risk of bleeding after surgery.[20]

In Japan, TXA is approved for treatment only not of systemic bleeding disorders but also disorders in which local hyperfibrinolysis may be involved. TXA can be given intramuscularly, intravenously, or orally. Adverse events reported to be associated with TXA treatment include anorexia, drowsiness, itching, rash, and a transient defect in color vision; such effects occur in <1% of patients.[22] In randomized studies, no marked increase in thrombosis after administration of TXA was observed, even in cases in which a thrombotic complication was anticipated and even when the agent was given during an operation.[23,24]

The plasma TXA concentration found to be effective in obtaining antifibrinolysis has been reported to range from 5 to 15 mg/L, and when 1300 mg TXA was given orally for 5 days, the peak plasma concentration was 16.4 mg/L.[24] In Japan, TXA is available in 250-mg capsules, and patients in the TXA group in our study took six of these daily. Overall, these patients had significantly greater aneurysm shrinkage than those not given TXA. Moreover, multivariant analysis found that TXA treatment was significantly associated with aneurysm shrinkage at 6 months after EVAR, and shrinkage of >4 mm was observed in 80% of patients without a type II endoleak. In the European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) study of EVAR outcomes, the maximum change in aneurysm diameter was <8 mm in 84% of 6337 patients without any detectable endoleaks.[25] Our findings suggest that antifibrinolytic therapy with TXA may be effective in achieving aneurysm shrinkage in such patients. Many patients with AAAs are receiving antiplatelet therapy for coexistent coronary artery or cerebral vascular disease. TXA may be especially useful in these patients by modifying the adverse effect of antiplatelet therapy on aneurysm shrinkage after EVAR without increasing the risk of thromboembolic complications.

Agents other than TXA that have been found to increase aneurysm shrinkage after EVAR include doxycycline,[26] a matrix metalloprotease inhibitor, statins,[27] and calcium channel blockers.[28] Perhaps a post-EVAR regimen combining antifibrinolytic therapy with one or more of these medications might be more effective in promoting AAA shrinkage. We found that administration of TXA alone was associated with aneurysm shrinkage only in patients who did not have a type II endoleak 6 months after EVAR.

Our study had the usual limitations of a nonrandomized investigation that included historical controls. We also did not evaluate the effect of TXA therapy on the coagulation and fibrinolysis systems by measuring levels of D-dimer, fibrin degradation products, and thrombin-antithrombin III complex. In addition, oral TXA therapy was started the morning after the EVAR procedure, but any blood trapped in the aneurysm sac would begin to clot just after stent graft deployment. Therefore, parenteral administration of TXA during EVAR, followed by oral administration afterward, might have been more effective.

CONCLUSIONS

Despite the limitations, we consider our results with TXA to be promising and suggest that studies to identify the dosage of the agent that is optimally safe and effective in obtaining aneurysm shrinkage after EVAR, as well as investigations of the most favorable timing and route (parenteral, oral, or a combination of the two) of TXA administration, are warranted.

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AUTHOR CONTRIBUTIONS

Conception and design: AA
Analysis and interpretation: AA
Data collection: AA, TS, SY, KS, HI, NM, SK, TY
Writing the article: AA
Critical revision of the article: KS, HI, SK, TY
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