Risk of recurrence of unusual site venous thromboembolism

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**Summary**

The term unusual site venous thrombosis defines uncommon clinical manifestations of venous thromboembolism occurring in sites different from the lower limbs or the lungs, with peculiar pathophysiological features and clinical history. Information on long-term outcomes of unusual site thrombosis is generally scant, because most studies are small and usually retrospective.

Recurrence rate of cerebral vein thrombosis is about 2/100 patient-years; the only identified predisposing factors have been male gender and personal history of thrombosis. Retinal vein occlusion showed a recurrence in the same eye of 2.5% and in the fellow eye of 11.9% within four years. Hypercholesterolemia, hypertriglycerideridemia and hyperhomocysteinemia were significantly associated with recurrent events. Recurrence rates of splanchnic vein thrombosis are difficult to estimate given the heterogeneity of patient populations; higher recurrence rates are reported in the cirrhotic population (from 27% to 38.5%). Hormone therapy, myeloproliferative neoplasms or other prothrombotic states, and absence of anticoagulant therapy are reported in the cirrhotic population (from 27% to 38.5%). Hormone therapy, myeloproliferative neoplasms or other prothrombotic states, and absence of anticoagulant therapy emerged as independent prognostic factors. Future studies should aim at better assessing the risk of recurrence in different patients subgroups and at identifying more accurate prognostic markers.

**Keywords**

Recurrence, cerebral vein thrombosis, retinal vein occlusion, splanchnic vein thrombosis

**Zusammenfassung**


**unusual site thromboses (UST)** represent uncommon and heterogeneous manifestations of venous thromboembolism (VTE). UST may involve any venous segment outside the veins of the lower limbs and the pulmonary arteries, including cerebral vein thrombosis (CVT), retinal vein occlusion (RVO) and splanchnic vein thrombosis (SVT).

Besides the presentation at unusual sites, UST shows peculiar pathophysiological and clinical features, mainly reflecting the different characteristics of the organs of origin. Moreover, significant heterogeneity exists in the short- and long-term prognosis of UST, both across the different clinical entities and within each of them. With respect to prognosis, one important aspect is represented by the risk of long-term recurrence, that may depend on the predisposing causes, thus potentially reflecting the clinical behaviour of thromboembolism occurring at usual sites, i.e. deep vein thrombosis (DVT) in lower limbs and pulmonary embolism (PE). Indeed, data from several studies show that lower limb DVT and/or PE occurring after non-oncological major surgery have the lowest risk of recurrence (about 1% per year) (1–2), whereas cancer-associated VTE has one of the highest (up to 15% per year) (3).

On the other hand, the recurrence rate after unprovoked VTE or VTE associated with minor risk factors remains quite heterogeneous, possibly ranging from 2–3% per year to up to 15–20% per year (4–6). Unfortunately, due to the lower frequency of diseases, the quality of data on the recurrence rate of UST is not as high as for lower limb DVT and PE.

This review aims at focusing on the most updated evidence on the risk of recurrence after UST and on its determi-
Cerebral vein thrombosis

Epidemiology

CVT is a rather uncommon disease (7). However, the recent introduction of noninvasive and highly sensitive diagnostic techniques, such as magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) has modified our knowledge of the spectrum of illness associated with CVT (7–8). CVT has an estimated annual incidence of:

- 3 to 4 cases per 2 million adults and
- 7 cases per 1 million neonates.

However, its exact incidence is unknown because of the lack of epidemiological studies (9).

Clinical presentation of CVT is highly variable with a remarkably wide spectrum of signs and modes of onset, thus mimicking numerous other disorders (9–10). The most common symptoms and signs are:

- headache and papilloedema, due to intracranial hypertension,
- seizures,
- focal neurological deficits and
- altered consciousness.

Headache occurs in 90% or more of patients. Papilloedema may occur in 30% of patients, and may cause visual loss and diplopia in case of compression of the sixth cranial nerve. Up to 40% of patients may have focal or generalized seizures or motor deficits. Conversely, symptoms such as dysarthria and aphasia are extremely uncommon.

Pathogenesis and risk factors

CVT usually affects young women, especially those on hormonal contraceptives. Several case-control studies and meta-analyses have found an association between CVT and many inherited and acquired thrombophilic abnormalities, including factor V Leiden, prothrombin G20210A mutation, deficiency of protein C, S and antithrombin, hyperhomocysteinemia and antiphospholipid syndrome (11).

Other established risk factors for CVT include tumours in the brain or in other sites, cerebral infections or traumas, pregnancy, puerperium (10). It was recently reported that JAK2 V617 mutation is not an uncommon finding in CVT patients, suggesting that this disease could be the first manifestation of a myeloproliferative neoplasm (MPN) although this remains controversial (12–13). In 15% to 20% of patients, CVT occurs in the absence of predisposing factors (10).

Natural history, risk of recurrence

The ability to accurately detect less clinically severe cases of CVT has changed our knowledge on the “natural history” of this disorder. In contemporary series, the reported mortality rate ranges between 8% and 14%, in contrast to prior studies where cause-specific mortality was as high as 30% to 50% (14). Several studies suggest that presence of intracranial haemorrhage at the time of diagnosis of CVT and epileptic seizures may be associated with an increased risk of poor outcome, defined as death or dependence.

Other potential predictors of poor outcome include old age, male sex, coma, mental status disorders, deep CVT, right intracranial haemorrhage, posterior fossa lesion, worsening of previous focal or de novo focal deficits, cerebral nervous system infection and cancer (14). On the other hand, young age and isolated intracranial hypertension at the time of diagnosis were found to be predictors of good outcome in some studies (14).

Recent guidelines recommend the use of unfractionated heparin or low-molecular-weight heparin followed by at least 3–6 months of oral anticoagulant therapy with vitamin K antagonists for most patients with a first episode of CVT (15–16). However, the optimal duration of anticoagulant treatment is not established, because little information is available on the long-term rate of recurrent CVT or VTE in other sites after the discontinuation of anticoagulant drugs (17).

The recurrence rate of CVT has been reported to be approximately 2/100 patient-years. Although information on recurrent CVT was ascertained in several studies (18–22), the validity of these findings is often limited by the modest sample size and by the retrospective or single-center design or single-country setting of the studies.

In a study that included a cohort of 77 patients with CVT, diagnosed between 1975 and 1990 and followed for a mean of 77.8 months, Preter and colleagues found a CVT recurrence in 11.7% of patients (18). In a more recent study, Ferro and co-workers (19) reported a much lower risk of recurrence. Fourteen patients (2.2%) out of 624 adults with a previous episode of CVT had a recurrent thrombosis over 16 months of follow-up. Of note, almost half (41.5%) of the recurrences occurred during anticoagulant treatment. These results were confirmed by a recently published study performed by Gosk-Bierska and colleagues in which the 154 patients included were followed up for a mean of 36 months (20). In this study, during the 464 patient-years of follow-up, there were 10 episodes of recurrent sinus thrombosis (2.2/100 patient-years). Of note, also in this study, the majority of recurrent events occurred within the first year and nine of these 10 events occurred while the patients were taking warfarin.

More recently, Martinelli et al. (21) found an event rate of 2.03 per 100 patient-years in a population of 145 patients with a first episode of CVT. Finally, our group conducted a multicenter retrospective study including 706 patients with a first episode with CVT (22). After a median follow-up of 40 months (range 6–297 months), CVT recurred in 31 patients (4.4%), while 46 patients (6.5%) had a VTE in a different site, arriving to an overall incidence of recurrence of 2.36 events per 100 patient-years; 95% confidence interval (CI) 1.78–2.87.

Three studies evaluated potential factors associated with recurrent thromboembolic events in patients with CVT (20–22). In the study by Gosk-Bierska et al. (20), no vari-
able was significantly associated with recurrent venous thrombosis in these patients, whereas in the study conducted by Martinelli et al. (21), risk factors for recurrent venous thrombosis were male gender and, for recurrence of VTE in other sites only, severe thrombophilia. In our study, only a personal history of previous VTE was associated with an increased risk of recurrence at multivariate analysis (22). Different results across the studies may be due to differences in patient selection and to the relatively small sample size of many studies.

Pathogenesis and risk factors

The pathogenesis of RVO is still unclear, although it is believed to follow the principles of Virchow’s triad: stasis, vessel wall damage and hypercoagulability (29). Arterial compression of the retinal veins, endothelial damage, and thrombosis may play different roles in different patients. Indeed, the thrombotic mechanism is necessarily the only underlying mechanism and "retinal vein occlusion" remains a more accurate, albeit unsatisfactory, definition of the disease than "retinal vein thrombosis". Furthermore, the pathogenesis and natural history of CRVO and BRVO are also likely to be different (30). Thus, it is first of all possible that different treatment strategies may actually be necessary for different clinical scenarios.

Both local and systemic risk factors have been associated with RVO. Open-angle glaucoma is the most frequent ophthalmologic disease that can predispose to RVO as it compromises venous outflow by increasing intra-ocular pressure through the lamina cribrosa. RVO is detected in 4–4.5% of eyes with primary open angle glaucoma, and primary open angle glaucoma or ocular hypertension in 4–43% of patients with RVO (31).

Among systemic risk factors, RVO has been associated with common cardiovascular risk factors such as hypertension and diabetes (32). In particular, more than 64% of RVO patients older than 50 years are hypertensive, and it is a predominant finding in recurrent RVO (88%) (33–36). Association between obesity and smoking and RVO is less consistent (34). Blood hyperviscosity is the probably main underlying mechanisms in patients with myeloprolifera-

Natural history, risk of recurrence and risk of cardiovascular disease

The natural history of retinal vein occlusion is highly variable (23, 27): Some cases show a favourable evolution with a progressive disappearance of haemorrhages, exudates and intraretinal oedema and a better visual outcome, while others develop severe complications like ocular neovascularization (proliferative retinopathy), vitreous haemorrhage, neovascular glaucoma and macular oedema. The worse clinical course of RVO, characterized by proliferative retinopathy and neovascular glaucoma, is associated with a more severe involvement of retinal circulation with a detection of larger ischaemic areas at the fluorescein angiography examination. Moreover, a poor prognosis has been associated with male gender, advanced age, and co-existence of multiple risk factors (39–40).

Although several data are available on short-term-prognosis, in particular on visual acuity, the rate of RVO recurrence is still poorly defined. Most of the studies have investigated RVO recurrence only as secondary outcomes. Moreover, several methodological drawbacks, such no data on type of RVO, bilateral involvement at the presentation, associated risk factors, and short follow-up, do not allow a precise estimate of RVO recurrence. Finally, some studies on natural history of RVO were performed in the 1970s and 1980s, when treatment of associated risk factors, such as hypertension, was not optional. For example, Michels and colleagues reported a 10% development of BRVO in the fellow eye over time (41). More recently, Hayreh
and colleagues (25) analyzed 1108 patients (1229 eyes) with various types of retinal vein occlusion: non-ischaemic and ischaemic central retinal vein occlusion, non-ischaemic and ischaemic hemiretinal vein occlusion, and major and macular branch retinal vein occlusion (25). The cumulative probability of developing a second episode of the same or a different type of retinal vein occlusion in the same eye was 0.9% within two years and 2.5% within four years, and in the fellow eye was 7.7% and 11.9%, respectively.

The natural history of BRVO and CRVO was recently summarized in two systematic reviews (42–43). A total of 24 eligible studies on BRVO and 53 on CRVO, were identified and reviewed, providing 1608 eyes with BRVO and 3271 eyes with CRVO for analysis on natural history (42–43). At baseline, 5% to 6% of eyes had bilateral BRVO, with 10% developing fellow eye involvement over an unknown length of time – based on the Michels and colleagues data (41, 42). At the time of presentation, bilateral CRVO was present in 0.4% to 43% of CRVO cases (43). Over various follow-up periods, 1.4% of CRVO cases developed a CRVO in the second eye over a 3-year period, 5% developed a BRVO in the second eye over a 30-month period, and 5% of CRVO cases developed any RVO over a 1-year period (43).

Risk factors for RVO recurrence are poorly defined. Sodi and colleagues have compared the prevalence of atherosclerotic and thrombophilic risk factors in a group of 17 patients with recurrent CRVO and 30 with a single episode of CRVO (44). At multivariate analysis, hypercholesterolemia (odds ratio (OR) 5.04, 95% CI 1.39–18.17), hypertriglyceridaemia (OR 5.60, 95% CI 1.52–20.61), fasting hyperhomocysteinaemia (OR 5.77, 95% CI 1.39–23.89), and postmethionine hyperhomocysteinaemia (OR 10.88, 95% CI 2.50–47.42) were found to be significantly associated with recurrent CRVO.

Only few studies have investigated the incidence rate of myocardial infarction and stroke in patients with a previous episode of RVO. Cugati and colleagues have assessed the incidence of cardiovascular and cerebrovascular mortality from two population-based cohort studies, the Beaver Dam Eye Study and Blue Mountains Eye Study (45). Vascular deaths were determined using either death certificates or the Australian National Death Index. Of 8384 baseline participants, 96 (1.14%) had RVO at baseline. Over 12 years, 1312 (15.7%) died of cardiovascular-related conditions and 341 (4.1%) died of cerebrovascular-related conditions. Age-standardized vascular mortality rates were 26.0% and 5.3%, respectively, in persons with RVO and 17.1% and 4.5%, respectively, in those without RVO. After adjusting for age, gender, body mass index, hypertension, diabetes, smoking, glaucoma, and study site, RVO was not associated with cardiovascular-related mortality (hazard ratio (HR) 1.2, 95% CI 0.8–1.8) or cerebrovascular-related mortality (HR 0.9, 95% CI 0.4–2.1) among participants of all ages. However, in persons aged less than 70 years, baseline RVO was associated with higher cardiovascular mortality (HR 2.5, 95% CI 1.2–5.2).

Khan and colleagues have recently tried to estimate the 10-year Framingham risk for patients with RVO in a systematic review (46). They have meta-analyzed six studies that reported baseline data on age, sex, smoking status, systolic blood pressure, total cholesterol, and high-density lipoprotein of RVO patients. The estimated 10-year Framingham risk score (FRS) in subjects with RVO was 10.1% (95% CI 9.9–10.2), which was significantly higher than the average FRS of 6% of the control group, the general Canadian population.

### Splanchnic vein thrombosis

#### Definition, classification and epidemiology

SVT involves veins draining from different abdominal organs, including small and large bowel, liver, spleen and pancreas. Budd-Chiari syndrome (BCS), portal vein thrombosis (PVT), mesenteric vein thrombosis (MVT) and splenic vein thrombosis (spVT) are different manifestations of SVT with peculiar characteristics (47).

SVT is the most common manifestation of unusual site VTE. However, it is frequently underdiagnosed, since clinical presentation is heterogeneous and there is a considerable rate of asymptomatic incidental findings.

PVT is the most common expression of SVT with epidemiological data ranging from a reported incidence of less than 4 cases per million people per year based on hospital registry in the 1980s (48) to a more recent population prevalence at autopsy of 1% (49). The incidence of MVT, identified through inpatient and autopsy registries, has been reported to be 2.7/100000 person-years (50). BCS is the least frequent manifestation of SVT, with an estimated incidence of about 1 case per million people per year (51) or even less in Asian countries (52). No accurate data are available on the epidemiology of spVT, which represents less than 10% of SVT in the general population (53). Multiple sites thrombosis accounts for almost 40% of SVT (53).

Incidental abdominal deep vein thrombosis, mainly located in the splanchnic veins, had an estimated prevalence of 1.74% (95% CI 1.29–2.34), in a recent retrospective review of 2591 abdominal computed tomography scans, performed for reasons other than the search of suspected SVT, during a 6-month period at a single institution (54).

#### Pathogenesis and risk factors

SVT may be associated with several underlying disorders, either local or systemic. The distribution of risk factors varies according to age, gender, geographical area and thrombosis location. Nonetheless, unprovoked thrombosis still account for at least 15% of patients (53).

A local precipitating factor is rare in BCS patients, while it is recognized in more than one-third of PVT patients (47). Hepatic cirrhosis and malignancies (mainly pancreatic, hepatobiliary or gastrointestinal) were the most frequent causes of PVT, being present in 34% and 31% of patients, respectively (53). A population-based study reported direct injury from surgery or inflammation and abdominal cancer as the most common local factors for MVT (50). Isolated spVT is provoked by acute or chronic pancreatitis in almost half of the patients (53); other frequent risk factors are cancer and splenectomy (53, 55).
MPN are the leading systemic cause of SVT, being diagnosed in half of BCS patients and one-third of extra-hepatic PVT (47).

Recently, the JAK2 V617F mutation, the main molecular marker of the Philadelphia-negative MPN, emerged as an independent factor for SVT (56–57). A meta-analysis reported a greater prevalence of JAK2 mutation in SVT patients compared with other site VTE, 32.5% (95% CI 25.5–35.9) vs 0.88% (95% CI 0.44–1.45) respectively, and found an increased risk of SVT associated with JAK2 mutation (OR 53.98, 95% CI 13.10–222.45) (58). Moreover, 52.4% (95% CI 38.0–66.5) of SVT patients with JAK2 mutation without overt MPN were diagnosed with a MPN during the follow-up period (58), suggesting that SVT may actually represent the first clinical manifestation of MPN.

Among inherited thrombophilia, a proper diagnosis of deficiencies of antithrombin, protein C and S is difficult, given the reduced synthesis of the natural anticoagulants in liver impairment (47). In patients with PVT, a recent meta-analysis showed a strong association with G20210A prothrombin mutation (OR 4.48, 95% CI 3.10–6.48) and a moderate association with factor V Leiden mutation (OR 1.90, 95% CI 1.25–2.90) (59). Conversely, in patients with BCS, a multicenter case-control study demonstrated a stronger association with factor V Leiden (relative risk (RR) 11.3, 95% CI 4.8–26.5) than with G20210A prothrombin mutation (RR 2.1, 95% CI 0.4–9.6) (60). Hormonal stimuli are common systemic risk factors for BCS. The use of oral contraceptive is more prevalent in Western countries, while pregnancy and puerperium have higher prevalence in Eastern countries (61). Less common risk factors include paroxysmal nocturnal hemoglobinuria (62) and Behcet’s disease (63).

**Natural history, risk of recurrence**

The natural history of SVT is unclear, because some form of therapy has been administered in all reported cohorts of patients. Long-term consequences include, among the others, hepatic cirrhosis in patients with BCS and portal hypertension in patients with PVT. Episodes of bleeding are quite common and may be related to underlying diseases, portal hypertension with esophageal varices and anticoagulant treatment. Moreover, as for any VTE event, also SVT patients are at increased risk of recurrences.

Although several studies investigated the short- and long-term prognosis of SVT, the risk of recurrence is still poorly defined and ranged from approximately 2–3/100 patient-years for venous thromboembolic events to more than 5/100 patient-years for both arterial and venous thrombotic events. The largest cohort of patients with SVT has been recently described in a retrospective study by Thatipelli et al. (53). They enrolled 832 patients with thrombosis of different splanchnic veins (including hepatic, splenic, portal or mesenteric) and different etiologies (notably, malignancy or cirrhosis in about 50%), diagnosed and followed up at a single institution, the Mayo Clinic, over a 20-year period. They also included a randomly selected control group of 236 patients with lower extremity DVT. During a mean follow-up period of 27 months, the incidence of recurrent venous thrombosis in patients with SVT was 3.5/100 patient-years. Half of the recurrent events involved the splanchnic venous system, while the other half involved limb veins or pulmonary arteries. Recurrence free survival at 10 year was comparable between patients with SVT and patients with DVT (74% vs 68%, p = 0.68) and was not improved by anticoagulant therapy. However, warfarin therapy was administered in 235 patients (28%), of whom 175 lifelong, but no information is provided on the use of alternative anticoagulant drugs such as heparins.

In the cohort by Amitrano et al. (64), 95 patients with SVT not associated with cancer or cirrhosis were followed for 41 months and 43.2% of them received lifelong oral anticoagulation. They observed a 10.5% incidence of new venous thrombotic episodes, mainly in the splanchnic area. However in this study lifelong anticoagulant therapy was protective (p = 0.005).

Condat et al. (65) described a retrospective cohort of 136 patients with non-malignant non-cirrhotic PVT, of whom 84 received anticoagulant therapy with heparin or vitamin K antagonists. During a median follow-up of almost four years, the global incidence of recurrent thrombotic events was 5.5/100 patient-years, including both venous and arterial thrombotic events. Anticoagulant therapy reduced the recurrence of thrombosis by two thirds and affected mainly the events within the portal venous system. Indeed, the incidence of recurrent PVT was 0.64/100 patient-years and 1.87/100 patient-years with and without anticoagulant therapy, respectively.

PVT that arises on underlying liver cirrhosis represents a particular entity and has been specifically evaluated in three recent cohort studies (66–68). Amitrano et al. (66) prospectively followed 39 patients with non-neoplastic PVT associated with cirrhosis. Anticoagulant treatment with enoxaparin was started in half of the patients at the time of diagnosis; the other half presented with gastro-esophageal bleeding, therefore anticoagulation was delayed until eradication of varices (median time from diagnosis 4 months). They reported 75% complete recanalization, in a median time of 6.5 months, and 27% recurrence of PVT in patients who achieved complete recanalization and stopped anticoagulation after at least six months of treatment.

In the retrospective cohort described by Delgado et al. (67), 55 patients with cirrhosis and PVT received anticoagulant therapy with low molecular weight heparin or vitamin K antagonists. Complete recanalization was achieved in 51.6% of patients with recent acute or subacute PVT after a median anticoagulation time of 6.1 months and in 37.5% of patients who initially presented with progression of a previous spleno-porto-mesenteric thrombosis after a median anticoagulation time of 7.35 months. Recurrent thrombosis in the splanchnic venous system occurred in 38.5% of patients who obtained complete recanalization and stopped anticoagulation therapy.

Senzolo et al. (68) enrolled 56 cirrhotic patients with PVT: 35 patients received the treatment protocol (anticoagulation with nadroparin or transjugular intrahepatic portosystemic shunting (TIPS) in those with contraindications to anticoagulation or when anticoagulation failed) and 21 pa-
tients, enrolled in another hospital, served as controls. PVT progression occurred in 15% of treated patients and in 71.4% of patients in the control group (p < 0.001), confirming that anticoagulation is a protective factor.

The high recurrence rate of these studies suggests that the presence of liver cirrhosis is a strong pathophysiological mechanism that might also be a risk factor for recurrent events, especially in the absence of anticoagulant treatment.

After a first initial episode of MVT, the recurrence rate of symptomatic VTE has been reported to be 2.34/100 patient-years in a multicenter cohort study on patients receiving secondary prevention with VKA (69). The risk of VTE recurrence was low during anticoagulant treatment and increased after discontinuation (from 1.05/100 patient-years to 4.59/100 patient-years, respectively).

Long-term prognosis of BCS is more difficult to assess, since patients not responding to anticoagulant treatment are managed with invasive procedures (such as angioplasty/stenting, TIPS and liver transplantation). In the largest cohort, 163 patients with non-malignant BCS described by the ENVIE study group (70), 86% were treated with anticoagulation, 34% with TIPS and 12% with liver transplantation. Survival rate was 87% at one year and 82% at two years. No information is available about the rate of recurrence in the general BCS population. For instance, in a small cohort of BCS patients undergoing liver transplantation, the incidence of recurrent BCS was 27%, same as was the incidence of other site VTE (including SVT and pulmonary embolism) (71).

Three studies evaluated potential factors associated with recurrence of VTE in patients with splanchnic vein thrombosis (53, 64–65). In the study by Thatipelli and coworkers (53), hormone therapy emerged as the only independent predictor of recurrence (HR 2.2, 95% CI 1.09–4.45), and factors associated with a marginally higher risk of recurrence were menopausal and hepatic vein thrombosis and multiple veins involvement. In the cohort described by Condat et al. (65) underlying prothrombotic state (including both thrombophilic abnormalities and MPN) and absence of anticoagulant therapy were independent predictors for recurrence; while in the study described by Amitrano et al. (64) the presence of MPN specifically emerged as a predictor for recurrence of VTE (p < 0.0001).

Conclusion

Unusual site thromboses are challenging manifestations of venous thromboembolic disease, with peculiar pathophysiology and heterogeneous clinical presentations. The risk of recurrence may vary considerably across different clinical entities, with high quality evidence on the long-term management substantially lacking in most cases.

Future studies should aim at better assessing the risk of recurrence in different patient subgroups, identifying accurate prognostic markers. This assessment should also take into account the consequences and case-fatality rates of recurrent thrombosis and bleeding in these specific settings. This will form the basis to stratify patients for their individual risks of recurrence and of treatment-associated adverse events, in order to provide the best antithrombotic therapy and to tailor its optimal duration.

Conflict of interest

The authors have no relevant conflict to declare in relation to this paper.

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