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Inferior vena cava agenesis in patients with lower limb deep vein thrombosis in the RIETE registry. When and why to suspect

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ABSTRACT

Background: Limited data exist about the clinical presentation and outcomes of patients with inferior vena cava agenesis (IVCA) who develop deep vein thrombosis (DVT).
Methods: We used the RIETE (Registro Informatizado Enfermedad Trombo Embólica) registry to compare clinical characteristics and outcomes of patients with lower limb DVT, according to the presence or absence of IVCA. Major outcomes included recurrent DVT, major bleeding and post-thrombotic syndrome (PTS).
Results: Among 50,744 patients with lower-limb DVT recruited in October 2018, 31 (0.06%) had IVCA. On multivariable analysis, patients aged < 30 years (odds ratio [OR]: 17.9; 95%CI: 7.05–45.3), with unprovoked DVT (OR: 2.49; 95%CI: 1.17–5.29), proximal (OR: 2.81; 95%CI: 1.05–7.53) or bilateral DVT (OR: 11.5; 95%CI: 4.75–27.8) were at increased risk to have IVCA. Patients with DVT and IVCA had lower odds to present with coexisting PE (OR: 0.22; 95%CI: 0.07–0.73). During the first year of follow-up, the rates of DVT recurrences (hazard ratio [HR]: 1.30; 95%CI: 0.07–6.43), pulmonary embolism (HR: 2.30; 95%CI: 0.11–11.4) or major bleeding (HR: 1.32; 95%CI: 0.07–6.50) were not significantly different with those with versus those without IVCA. One year after the index DVT, IVCA patients had a higher rate of skin induration (OR: 3.70; 95%CI: 1.30–9.52), collateral vein circulation (OR: 3.57; 95%CI: 1.42–8.79) or venous ulcer (OR: 5.87; 95%CI: 1.36–1.87) in the lower limb than those without IVCA.
Conclusions: Certain clinical features such as unprovoked and bilateral proximal DVT in young patients should raise the suspicion for IVCA. Patients with IVCA had higher odds for symptoms of post-thrombotic syndrome.
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1. Introduction

Congenital anomalies of the inferior vena cava have been reported in 0.1–8.7% of the general population [1], and inferior vena cava agenesis (IVCA) has been found in around 5% of young adults presenting with unexplained deep vein thrombosis (DVT) in the lower limbs [2,3]. The IVCA results from aberrant development of the vein during embryogenesis, and may be complete or segmental. Another hypothetic cause of

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IVCA may be an intrauterine thrombosis of the vena cava or a thrombosis during the perinatal period, with obliteration and subsequent reabsorption of the vein [1].

Compression ultrasonography (CUS) may be useful to find IVCA by revealing the presence of collateral veins in the abdomen, but it may miss and underdiagnose many patients with IVCA. The gold standard of imaging for diagnosis of IVCA are computed tomography or magnetic resonance imaging (MRI) studies, which are not routinely performed in patients with DVT [2–6]. Because of the uncommonness of IVCA, as well as limited use of confirmatory imaging studies in many DVT patients, data related to the clinical presentation and outcomes of patients with IVCA who develop DVT remain sparse. Insights into the natural history of the disease and outcomes in this patient subgroup are critical, as there may have implications for treatment options.

The Registro Informatizado de Enfermedad Trombo Embólica (RIETE) is an ongoing, multicenter registry of consecutive patients with acute venous thromboembolism (VTE), with 223 collaborating centers all over the world (ClinicalTrials.gov identifier: NCT02832245) [7–10]. The rationale and methodology of the registry has been previously reported elsewhere [11]. In this study, we used data from RIETE to describe the clinical characteristics and outcomes of DVT patients with diagnosed IVCA. We compared the results with the rest of DVT patients in RIETE to provide clinical context.

2. Methods

2.1. Patients

For this study, we included all patients presenting with acute, symptomatic DVT in the lower limbs, confirmed by objective tests (compression ultrasonography [CUS] or contrast venography) from March 2001 to October 2018. IVCA was defined as a segmental or total absence of the inferior vena cava, as found on contrast venography, CT-scan or MRI. Patients were excluded if they were participating in a therapeutic clinical trial taking a blind medication. All patients provided oral or written informed consent to their participation in the registry, according to the requirements of the ethics committees within each enrolling center. All patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention.

2.2. Study endpoints

The main outcomes of the study were: 1) the rate of DVT recurrences, symptomatic pulmonary embolism (PE) or major bleeding appearing during the first year of follow-up; and 2) the development of signs or symptoms of post-thrombotic syndrome (PTS) in the DVT-affected leg 12-, 24- and 36 months after the index DVT diagnosis, as assessed by a physician trained in the management of vascular diseases.

2.3. Variables

The following parameters were recorded in RIETE: clinical status including coexisting conditions such as chronic heart or lung disease, recent bleeding, anemia or renal insufficiency; risk factors for VTE; the treatment received upon VTE diagnosis and outcomes. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with or without bathroom privileges) for ≥4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE. Active cancer was defined as newly diagnosed cancer or when receiving anti-neoplastic therapy of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support or combined therapies). Unprovoked VTE was considered in the absence of active cancer, recent immobility, surgery, estrogen use, pregnancy, postpartum or recent long-term travel. Recent bleeding was considered in patients having suffered major bleeding <30 days prior to VTE. Anemia was defined as hemoglobin levels < 13 g/dL for men and <12 g/dL for women. Creatinine clearance levels were measured using the Cockroft-Gault formula.

2.4. Population and follow up

All patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. All patients were followed-up for at least 3 months. During follow-up, special attention was paid to any signs and/or symptoms suggesting recurrent DVT, PE, major bleeding or PTS signs. Each episode of clinically suspected recurrent DVT or PE was documented by repeat objective imaging. Bleeding complications were classified as 'major' if they were overt and required a transfusion of 2 units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal [11]. Fatal bleeding was defined as any death occurring <10 days after a major bleeding episode, in the absence of any alternative cause of death. Fatal PE, in the absence of autopsy, was defined as any death appearing <10 days after PE diagnosis, in the absence of any alternative cause of death. Signs of PTS were collected at the study centers at 12-, 24- and at 36 months. They are the same items than those required for the Villalta score, the recommended tool to assess PTS by the International Society of Thrombosis and Haemostasis [12].

2.5. Statistical analyses

Categorical variables were compared using the chi-square test (two-sided) and Fisher's exact test (two-sided). Continuous variables were compared using Student *t*-test. First, we examined the relationship between the clinical characteristics at baseline and the diagnosis of IVCA using a logistic regression model. Any variable achieving a p-value of <0.10 on bivariate analysis was included in the multivariable analysis. Then, the incidence rates of VTE recurrences, symptomatic PE events, major bleeding or death appearing during follow-up were calculated and compared using the hazard ratios (HR) and 95% confidence intervals (CI). Finally, we assessed for signs of PTS among patients who attended follow-up visits at 12, 24 and at 36 months, and compared their presence or absence according to the existence of IVCA. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program (version 21.0. for Windows, 2004 SPSS Inc. Chicago, Illinois, US).

3. Results

As of October 2018, 50,744 patients with acute symptomatic DVT in the lower limbs were recruited, of whom 31 (0.06%) were diagnosed with IVCA. IVCA was detected during the index hospitalization in 24 patients (using CT-scan in 19, MRI in 3, contrast venography in 2), and was already known from prior encounters in 7 patients with prior DVT. Patients with IVCA were much younger than those without IVCA (mean and standard error of the mean: 37 ± 3.2 vs. 65 ± 0.1 years; $p < 0.001$), more likely to be men (odds ratio [OR]: 2.77; 95%CI: 1.24–6.20), more likely to have proximal DVT (all patients with IVCA had proximal DVT, as compared to 83% of those without IVCA) or bilateral DVT (OR: 18.6; 95%CI: 8.56–40.6) and less likely to have concomitant PE (OR: 0.22; 95%CI: 0.07–0.73) at baseline than those without IVCA (Table 1). They also were less likely to have active cancer (OR: 0.12; 95%CI: 0.02–0.89) or recent immobility (OR: 0.23; 95%CI: 0.06–0.98), and more likely to have unprovoked DVT (OR: 2.66; 95% CI: 1.22–5.77) or prior DVT (OR: 2.37; 95%CI: 1.12–5.04) than those without IVCA. There were no differences in thrombophilia testing.

On multivariable analysis, after adjusting for patient's gender, age, site of the DVT (proximal vs. distal), sidedness (uni- vs. bilateral), concomitant diseases, risk factors for DVT (cancer, transient risk factors or unprovoked), anemia and renal function, only age < 30 years (OR: 17.9; 95%CI: 7.05–45.3), unprovoked DVT (OR: 2.49; 95%CI:

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Table 1
Clinical characteristics of 50,744 patients with lower limb DVT, according to presence or absence of inferior vena cava agenesis.

	IVC agenesis	No IVC agenesis	Odds ratio (95%CI)
Patients, N	31	50,713	
Clinical characteristics			
Male gender	23 (74%)	25,833 (51%)	2.77 (1.24–6.19)
Mean age (years ± SD)	37 ± 18	65 ± 17	–
Age < 30 years	15 (48%)	2064 (4.1%)	22.1 (10.9–44.8)
Age 31–50 years	7 (23%)	8448 (17%)	1.46 (0.63–3.39)
Initial DVT presentation			
Any DVT, and coexisting PE	3 (9.7%)	16,542 (32%)	0.22 (0.07–0.73)
Isolated proximal DVT	28 (90%)	28,506 (56%)	7.27 (2.21–23.2)
Proximal DVT and PE	3 (9.7%)	13,668 (27%)	0.29 (0.09–0.96)
Isolated distal DVT	0	5634 (11%)	–
Distal DVT and PE	0	2874 (5.7%)	–
Lower limb DVT, bilateral	9 (29%)	1081 (2.1%)	18.8 (8.63–40.9)
Diagnosis of DVT			
Compression ultrasound	29 (97%)	48,899 (97%)	1.01 (0.14–7.40)
Contrast venography	2 (6.5%)	1035 (2.3%)	3.31 (0.53–11.8)
Magnetic resonance angiography	3 (9.7%)	141 (0.31%)	38.4 (9.18.116)
Computed tomography scan	19 (61%)	2379 (5.9%)	32.2 (15.6–68.3)
Risk factors			
Active cancer	1 (3.2%)	10,915 (22%)	0.12 (0.02–0.89)
Immobility ≥ 4 days	2 (6.5%)	11,545 (23%)	0.23 (0.06–0.98)
Surgery	4 (13%)	5177 (10%)	1.30 (0.46–3.73)
Estrogen use	3 (9.7%)	2621 (5.2%)	1.97 (0.60–6.47)
Pregnancy or postpartum	1 (3.2%)	701 (1.4%)	2.38 (0.32–17.5)
None of the above (unprovoked)	22 (71%)	24,306 (48%)	2.66 (1.22–5.77)
Prior VTE	10 (32%)	8476 (17%)	2.37 (1.12–5.04)
Co-morbidities			
Chronic lung disease	1 (3.2%)	5018 (9.9%)	0.30 (0.04–2.23)
Chronic heart failure	0	2696 (5.3%)	–
Anemia	11 (35%)	16,977 (33%)	1.09 (0.52–2.28)
Platelet count < 100,000/μL	0	1302 (2.6%)	–
CrCl levels < 50 mL/min	0	11,584 (23%)	–
Thrombophilia testing, N			
Patients tested, N	15	10,823	
Factor V Leiden	3 (20%)	1432 (13%)	1.64 (0.46–5.82)
Prothrombin mutation	1 (6.7%)	1061 (9.8%)	0.66 (0.09–5.00)
Protein C deficiency	0	177 (1.6%)	–
Protein S deficiency	0	455 (4.2%)	–
Antithrombin deficiency	0	162 (1.5%)	–
Antiphospholipid syndrome	1 (6.7%)	905 (8.4%)	0.78 (0.10–5.96)

Abbreviations: DVT, deep vein thrombosis; IVC, inferior vena cava; SD, standard deviation; IQR, inter-quartile range; PE, pulmonary embolism; VTE, venous thromboembolism; CrCl, creatinine clearance; CI, confidence intervals.

1.17–5.29), proximal DVT (OR: 2.81; 95%CI: 1.05–7.53) and bilateral DVT (OR: 11.5; 95%CI: 4.75–27.8) showed significantly increased odds for IVCA.

The duration of anticoagulant therapy was longer in patients with IVCA than in those without IVCA (median, 736 vs. 179 days, respectively), and 74% of patients with IVCA were still receiving anticoagulation one year after DVT diagnosis (Table 2). Low-molecular-weight heparin was the most often used drug for initial therapy in both subgroups (71% vs. 89%). During the first year of follow-up, one patient with IVCA developed recurrent DVT, one had a symptomatic PE and one suffered major bleeding. The rates of DVT recurrences (hazard ratio [HR]: 1.30; 95%CI: 0.07–6.43), symptomatic PE (HR: 2.30; 95% CI: 0.11–11.4) or major bleeding (HR: 1.32; 95%CI: 0.07–6.50) were not significantly different in those with compared with patients without IVCA (Table 3). No patient with IVCA died. After adjusting for percent time of anticoagulation, the risk for DVT recurrences (HR: 1.75; 95%CI: 0.25–12.4), symptomatic PE (HR: 2.61; 95%CI: 0.37–18.6) or major bleeding (HR: 1.72; 95%CI: 0.24–12.3) remained without differences.

Assessment for PTS signs in the affected leg was performed 12 months after DVT diagnosis in 20 patients with IVCA and in 3671 without IVCA. At 12 months, patients with IVCA had a higher odds of manifesting skin induration (OR: 3.70; 95%CI: 1.30–9.52), collateral venous circulation (OR: 3.57; 95%CI: 1.42–8.79) or venous ulceration (OR: 5.87; 95%CI: 1.36–1.87) than those without IVCA (Table 4). Similarly, in an exploratory analysis among patients with available follow-up data three years after DVT, 5 of 12 (42%) patients with IVCA and 97 of 1537 (6.3%) without IVCA that were assessed for PTS had developed a venous ulcer (OR: 10.6; 95%CI: 3.02–34.8).

Table 2
Treatment strategies and outcomes in patients with- vs. without inferior vena cava agenesis.

	IVC agenesis	No IVC agenesis	Odds ratio (95% CI)
Patients, N	31	50,713	
Initial therapy			
Low-molecular-weight heparin	22 (71%)	45,112 (89%)	0.30 (0.14–0.66)
Mean LMWH doses (IU/kg/day)	172 ± 44	174 ± 42	–
Unfractionated heparin	2 (6.5%)	2439 (4.8%)	1.37 (0.33–5.72)
Thrombolytics	0	494 (0.97%)	–
Fondaparinux	2 (6.5%)	1107 (2.2%)	3.09 (0.74–13.0)
Direct oral anticoagulants	2 (6.5%)	1146 (2.3%)	2.98 (0.71–12.5)
Inferior vena cava filter	0	1531 (3.0%)	–
Mechanical thrombolysis	0	88 (0.81%)	–
Surgical intervention	0	16 (0.14%)	–
Long-term therapy			
Vitamin K antagonists	17 (55%)	31,412 (62%)	0.75 (0.37–1.51)
Low-molecular-weight heparin	6 (19%)	14,006 (28%)	0.63 (0.26–1.53)
Mean LMWH doses (IU/kg/day)	143 ± 52	148 ± 47	–
Direct oral anticoagulants	7 (23%)	3502 (6.9%)	3.93 (1.69–9.13)
Surgical intervention	0	13 (0.11%)	–
Duration of anticoagulation			
Mean days (±SD)	1105 ± 101	280 ± 41	–
Median days (IQR)	736 (373–1599)	179 (101–293)	
Duration of follow-up			
Mean days (±SD)	1105 ± 101	377 ± 55	–
Median days (IQR)	736 (373–1599)	171 (56–471)	

Abbreviations: IVC, inferior vena cava; CI, confidence intervals; LMWH, low-molecular-weight heparin; IU, international units; SD, standard deviation; IQR, inter-quartile range.

4. Discussion

To our knowledge, this manuscript describes the largest cohort of patients with IVCA presenting with acute lower-limb DVT. Our study confirms that young age, unprovoked DVT, especially if proximal and bilateral, should raise the suspicion of IVCA. This is in line with prior reports in the literature, suggesting that patients with lower limb DVT and IVCA are typically young, most likely men, more likely to have unprovoked proximal DVT, and less likely to have coexisting PE

Table 3
Clinical outcomes during the first year after DVT.

	IVC agenesis	No IVC agenesis
Patients, N	31	50,713
Duration of therapy		
Median days (IQR)	1054 (437–1739)	224 (119–484)*
Clinical outcomes		
Recurrent DVT; N (%; 95%CI)	1 (3.23%; 95%CI: 0.16–14.9)	1237 (2.44%; 95%CI: 2.31–2.58)
Subsequent PE; N (%; 95%CI)	1 (3.23%; 95%CI: 0.16–14.9)	710 (1.40%; 95%CI: 1.30–1.51)
Subsequent PE in patients with proximal DVT; N (%; 95%CI)	1 (3.26%; 95%CI: 0.16–16.1)	614 (1.47%; 95%CI: 1.36–1.59)
Major bleeding; N (%; 95%CI)	1 (3.23%; 95%CI: 0.16–14.9)	1255 (2.47; 95%CI: 2.34–2.61)
All-cause death; N (%; 95% CI)	0	4996 (9.85%; 95%CI: 9.59–10.1)

Abbreviations: DVT, deep vein thrombosis; IQR, inter-quartile range; CI, confidence intervals; PE, pulmonary embolism; IVC, inferior vena cava.
* $p < 0.001$.

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Table 4
Signs and symptoms of post-thrombotic syndrome 12, 24 and 36 months after DVT diagnosis, according to presence or absence of inferior vena cava agenesis.

	12 months		24 months		36 months	
	IVC agenesis	No IVC agenesis	IVC agenesis	No IVC agenesis	IVC agenesis	No IVC agenesis
Patients, N	20	3671	10	2120	12	1537
Pain	3 (15%)	575 (16%)	2 (20%)	306 (14%)	3 (25%)	247 (16%)
Cramps	3 (15%)	448 (12%)	1 (10%)	322 (15%)	2 (17%)	256 (17%)
Heaviness	10 (50%)	985 (27%)*	4 (40%)	566 (27%)	7 (58%)	423 (28%)*
Itching	2 (10%)	271 (7.4%)	2 (20%)	165 (7.8%)	1 (8.3%)	136 (8.8%)
Paresthesia	3 (15%)	408 (11%)	1 (10%)	302 (14%)	2 (17%)	211 (14%)
Edema	10 (50%)	1197 (33%)	4 (40%)	705 (33%)	5 (42%)	485 (32%)
Skin induration	6 (30%)	381 (10%)*	2 (20%)	239 (11%)	4 (33%)	238 (15%)
Hyperpigmentation	5 (25%)	599 (16%)	3 (30%)	431 (20%)	5 (42%)	386 (25%)
Collateral venous circulation	9 (45%)	684 (19%)†	5 (50%)	403 (19%)*	8 (67%)	355 (23%)†
Erythema	1 (5.0%)	267 (7.3%)	1 (10%)	176 (8.3%)	3 (25%)	142 (9.2%)
Pain during calf compression	1 (5.0%)	322 (8.8%)	0	230 (11%)	1 (8.3%)	181 (12%)
Venous ulcer	3 (15%)	107 (2.9%)*	4 (40%)	91 (4.3%)‡	5 (42%)	97 (6.3%)‡

Patients with IVC agenesis are used as the reference subgroup for comparisons: *$p < .05$; †$p < .01$; ‡$p < .001$.
Abbreviations: DVT, deep vein thrombosis; IVC, inferior vena cava.

[2,4–6,13–22]. Findings of this study and prior reports, collectively, hint that presence of unprovoked, particularly proximal and/or bilateral, DVT in young patients should raise the suspicion for IVCA and may require additional imaging.

Giving the rarity of the disease, there is no evidence based approach to management. In our cohort, patients with IVCA were less likely to have concomitant PE at baseline than those without IVCA, but we failed to find differences in the risk for subsequent DVT or PE during follow-up, most likely because of the sample size. Most experts choose to focus the management towards the prevention of DVT recurrences. Some studies have suggested the potential utility of thrombolytic therapy or even thrombectomy in DVT patients with IVCA [13,21,23–25]. Other studies reported a higher risk for DVT recurrences and suggested to prolong the duration of anticoagulant therapy [6,13,26]. No patient with IVCA in our cohort underwent thrombolytic therapy or surgical thrombectomy. What we found was a higher risk to develop severe PTS signs (pigmentation and venous ulcers) in patients with IVCA during follow-up, consistent with prior reports [21,27]. The higher incidence of severe signs of PTS, particularly when most of the patients were young, warrants early detection of IVCA in at-risk patients presenting with DVT. Whether these patients benefit from thrombolytic therapy or surgical thrombectomy is a matter of controversy, and warrants additional dedicated studies.

Our study has a number of limitations. First, the proportion of patients with IVCA in our cohort was most likely conservative because some cases might have been missed by an incomplete radiological investigation or inadequate awareness of the possible causative relationship of an IVCA with DVT. CUS is usually the first imaging modality in the evaluation of patients with suspected DVT, but anomalies of the IVC may be missed on CUS. We hope that investigations like ours raise the awareness of the practitioners to consider IVCA in appropriate clinical scenarios. Second, our study was not designed for assessment of comparative effectiveness of management strategies in patients with IVCA. Since all patients with IVCA in our cohort received standard anticoagulant therapy and none received thrombolytic therapy or thrombectomy, we are unable to comment on the potential utility of more aggressive therapies. However, our study provides important insights into the long-term outcomes of DVT patients with IVCA. Third, RIETE is a large multinational registry developed with the aim of generating knowledge to help patients, clinicians, and policymakers to make more informed decisions about venous thromboembolic disease. The registry does not provide financial incentives (funding support) for patient enrollment. As such, we were unable to provide complete follow-up data for all long-term outcomes. Despite this limitation, the data remain as the largest series of patients in the literature – and within some confidence limits – provide interim approximation of the long-term symptoms for these patients. Fourth, given the small number of events in patients with IVCA during follow-up, additional studies are required to provide accurate estimates of risk, compared with other patient subgroups. Importantly, we noted that coexisting PE is much less likely for DVT patients with IVCA, compared with those without IVCA (Table 1). Fifth, venous anomalies, including IVC agenesis has been reported to correlate with splenic anomalies including splenic agenesis or, in turn, polysplenia. RIETE, by design, however, does not systematically gather information related to non-cardiac computed tomography findings, including splenic findings. Finally, although many of the studies from the RIETE registry were designed with broad or detailed a priori plans, IVCA is a rare phenomenon and the decisions to explore several of the data elements (including signs of venous insufficiency one year after presentation) were based on post-hoc plans and analyses. However, to our knowledge, these data represent the largest series of data for patients with IVCA. Future dedicated multicenter studies could be designed to provide more precise estimates about the long-term treatment patterns and sequelae of patient with IVCA who suffer from VTE.

In summary, presence of unprovoked DVT, proximal DVT and bilateral DVT were associated with increased odds of IVCA. DVT patients with IVCA had a remarkably lower odds to present with coexisting PE (OR: 0.22, 95% CI: 0.07–0.73). The long-term event rates were low in patients with IVCA and not significantly different from the rest of the patients. However, DVT patients with IVCA were more likely to develop severe signs of post-thrombotic syndrome than those without IVCA. This should lead to increase awareness about IVCA in young patients presenting with bilateral, unprovoked DVT in the lower limbs.

Disclosures

Dr. Bikdeli reports that he is a consulting expert (on behalf of the plaintiff) for litigation related to a specific type of inferior vena caval filters.

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Appendix A

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