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Supplemental table 1. Case reports of thrombosis in patients with afibrinogenemia, dysfibrinogenemia, hypodysfibrinogenemia or unspecified fibrinogen deficiency, or hypofibrinogenemia

Authors	Patient age	Patient sex	Diagnosis	Gene(s) affected	Description of thrombotic event(s)	Treatment of thrombotic event(s)	Prevention of thrombotic events	Other notes
Castaman et al. 2009 [17]	39	F	Afibrinogenemia	FGG	Acute occlusion of the anterior branch of the left renal artery	Birth control (estroprogestinic pill) was stopped and patient received low molecular weight heparin (enoxaparin 40 mg daily) and fibrinogen for 6 days	Leuprorelin acetate (single dose of 11.25 mg every 3 months, for 6 months)	-
Chapin et al. 2013 [45]	33	F	Afibrinogenemia	-	Bilateral segmental and subsegmental pulmonary emboli	Unfractionated heparin, transitioned to enoxaparin (1 mg/kg) twice daily for 4 months	Enoxaparin 40 mg twice a week	Thrombosis occurred 6 months after placement of a peripherally inserted central catheter and 3 weeks after placement of a port-catheter. Patient was receiving levonogestrel-ethinyl estradiol medication for menorrhagia. Fibrinogen concentrate treatment (Riastap, 50 mg/kg bi-weekly) was continued unchanged after thrombosis
Chevalier et al. 2011 [8]	37	M	Afibrinogenemia	FGA	Distal deep vein thrombosis in the left tibial and fibular veins	Low molecular weight heparin (4,750 UI every 12 h, subcutaneous); second occurrence treated by lowering target fibrinogen level	-	Fibrinogen concentrate treatment before and after thrombosis, because of previous occurrence of cerebral hematoma

Chun et al. 2005 [20]	22	M	Afibrinogenemia	-	<p>1. Thrombosis in left internal carotid artery resulted in thrombotic stroke/infarct in the middle cerebral artery territory.</p> <p>2. Subsequently from coronary ostia down the left main coronary artery (immediately after surgery for aortic valve vegetation); thrombectomy was required</p> <p>3. Subsequently (post-op) venous thromboembolism in the right subclavian vein, axillary vein, right internal jugular vein, and superior vena cava, probably attributable to indwelling lines</p>	Unfractionated heparin	Low molecular weight heparin	<p>1. Left Internal carotid thrombosis occurred spontaneously.</p> <p>2. Transesophageal echocardiogram study showed vegetation on aortic valve leaflets; patient underwent cardiopulmonary bypass surgery and the vegetation that turned out to be fibrinous material.</p> <p>3. Venous thromboembolism: developed after cardiopulmonary bypass surgery with perioperative fibrinogen replacement therapy to maintain plasma level 0.6–1.0 g/l; pre-operatively 10 g administered to reach a level of 2.3 g/l; fibrinogen replacement therapy was continued after detection of thrombosis</p>
Cronin et al. 1988 [46]	24	F	Afibrinogenemia	-	Multiple pulmonary emboli	Anovulant, TXA and cryoprecipitate infusions were discontinued; a filter was placed in the inferior vena cava	-	Patient underwent right subtalar and left ankle joint fusion. Cryo administered peri- and post-operatively to keep fibrinogen levels above 1.0 g/l

De Mattia et al. 1993 [43]	13	F	Afibrinogenemia	-	Ischemic-thrombotic pathology of toes on the right foot (two presentations)	After first presentation, substitutive therapy with lyophilised fibrinogen and/or plasma; after second presentation, FFP (10 ml/kg), low-dose heparin (4 UI/kg) and hemorrheologic and vasodilative drugs (pentoxifylline, nifedipine, LMW dextran 40) - leading to complete recovery in 3 months	-	After first presentation: extensive period of marching
Dickenman et al. 1955 [47]	39	F	Afibrinogenemia	-	Swelling of right leg due to thrombophlebitis; swelling of left leg due to thrombophlebitis; occlusion of left femoral artery; occlusion of right brachial artery; thrombus in the right iliac artery; a few small thrombi in the arterioles and capillaries of the lungs		-	Patient was in good health but had received x ray and radium therapy for cervix uteri carcinoma 2 years previously. The patient's death was attributable to thrombosis
Haberer et al. 2008 [19]	30	F	Afibrinogenemia	-	Thrombosis of left fibular veins	Compressive stockings	-	Patient underwent surgery (enucleation of the right eye). Fibrinogen concentrate (Clottagen, daily doses 4.5 + 1.5 + 1.5 g) was given perioperatively. Events occurred 1 day after last dose Anticoagulation was not started after thrombosis due to risk of bleeding

Henselmans et al. 1999 [32]	22	F	Afibrinogenemia	-	Multiple pulmonary emboli	Low molecular weight heparin (15,000 anti-factor Xa activity units twice daily, for 3 months) and cryoprecipitate (maintenance dose); for subsequent episode of PE, low molecular weight heparin for 12 months	-	Following initial occurrence of pulmonary embolism, the patient was treated with a maintenance dose of cryoprecipitate. Subsequent pulmonary embolism occurred within 24 h of an infusion of cryoprecipitate, but home fibrinogen substitution was continued after thrombosis (cryoprecipitate replaced with fibrinogen concentrate, 4.5 then 3.5 g twice per week)
Kumar et al. 2008 [40]	27	M	Afibrinogenemia	-	Right ventricular myocardial infarction	Dual antiplatelet therapy (aspirin plus clopidogrel), statins and angiotensin converting enzyme inhibitors	-	-
Lebreton et al. 2015 [9]	32	F	Afibrinogenemia	FGA	Pulmonary embolus and distal DVT in the right leg	Enoxaparin 0.5 mg/kg twice a day and fibrinogen concentrate replacement (target level 1.5 g/l) every 2 days	-	Thrombosis diagnosed 17 days post-partum. Fibrinogen concentrate (Clottagen) was given for maintenance of 1 g/l in plasma during pregnancy and 2 g/l for caesarean section; 1.5 g administered 2 days after delivery. Patient was heterozygous for the factor V Leiden mutation
MacKinnon and Fekete 1971 [48]	36	F	Afibrinogenemia	-	Post-mortem examination revealed thrombi in lungs and internal carotid artery; previously, painful foot, cold/blue/gangrenous toes	-	-	Recurring hemorrhages were treated with whole blood transfusions and fibrinogen when it became available. Patient was taking oral contraceptive medication

Margaglione et al. 2015 [38]	37	F	Afibrinogenemia	FGA	Thrombosis in the right transverse sinus and left internal jugular vein	Rivaroxaban (20 mg/day for 4 weeks; 7.5 mg/day thereafter)	Rivaroxaban 7.5 mg/day	Fibrinogen concentrate treatment was continued after thrombosis as the patient previously suffered cerebral hemorrhage
Matsumoto et al. 2008 [49]	35	F	Afibrinogenemia	-	Thrombus in inferior vena cava and pulmonary embolism	Inferior vena cava filter; subcutaneous unfractionated heparin 20,000 U per day for 2 weeks and 12,500 U per day for the following 2 weeks	Warfarin 2 or 3 mg/day; fibrinogen concentrate 2 g every 2 weeks	Patient treated with fibrinogen for cerebral hemorrhage before onset of thrombosis. Thrombosis related to placement of a femoral central catheter
Mukaddam et al. 2015 [50]	28	F	Afibrinogenemia	FGB	Thrombosis in the portal, splenic and right hepatic vein	-	-	Patient had received cryoprecipitate and fresh frozen plasma for surgery a year before
Ozdemir et al. 2015 [18]	23	F	Afibrinogenemia	-	Bilateral ischemic lesions on foot and ankle that required amputation. Subsequently in the right arm	Amputation, followed by subcutaneous enoxaparin, aspirin (antiagregan dosage) and nifedipine; fibrinogen replacement was continued. After subsequent episode of thrombosis, treatment was heparin and aspirin, followed by aspirin and low molecular weight heparin	-	Patient received fibrinogen replacement prior to the right arm thrombosis but not before the initial thrombosis Fibrinogen was continued after thrombosis due to risk of bleeding
Pati et al. 2009 [51]	32	F	Afibrinogenemia	-	Bilateral pulmonary emboli and "free floating" inferior vena cava thrombus	-	Caval filter	Fibrinogen concentrate (Haemocomplettan P, 2 g every 2 days) was given for severe hemorrhage prior to onset of thrombotic events. Due to risk of bleeding, anticoagulation therapy was not initiated after thrombosis
Roqué et al. 2004 [52]		F	Afibrinogenemia	-	Thrombosis of the renal and gonadal veins. Upper lobe infiltrate on chest x-ray.	Unfractionated heparin (14 - days) and cryoprecipitate		Symptoms developed after the patient gave birth for the second time

Sartori et al. 2015 [16]	48	F	Afibrinogenemia	-	Extended thrombosis of abdominal aorta with peripheral embolism	Fibrinogen concentrate (maintain fibrinogen above 0.8 g/l), aspirin (50 mg every other day) and enoxaparin (75 U/kg bid)	Low-dose aspirin and fibrinogen concentrate 2 g every 5 days	Fibrinogen concentrate given as long-term prophylaxis following cerebral hemorrhage 10 years before thrombosis. Fall with low back trauma and haematoma of left elbow and buttock a few months before thrombosis; treated with FC (1 g i.v. every 3–4 days for 14 days). Fibrinogen was continued after thrombosis
Schuepbach et al. 2004 [15]	44	M	Afibrinogenemia	FGA	Thrombus in left anterior tibial artery; four relapses are documented	Local lysis using urokinase	LMWH (Fragmin, initially 5,000 IU twice daily subcutaneously; dose doubled after first relapse), aspirin (100 mg daily) and fibrinogen replacement therapy; lepirudin (bolus 0.4 mg/kg then 0.5 mg/kg/h) used to replace LMWH after third relapse (fibrinogen concentrate and aspirin continued); lepirudin replaced by unfractionated heparin after 9 days; lepirudin re-introduced after 4 th relapse and then replaced by UFH then LMWH	Haemocomplettan 4 g/week administered since cerebral haemorrhage at age 23

Simsek et al. 2008 [53]	24	M	Afibrinogenemia	-	Cyanosis of fingers; subsequent occlusion of right and left pulmonary arteries; subsequent carotid artery infarction. History of popliteal DVT	Iloprost; then enoxaparin (80 mg/day); then enoxaparin with aspirin	Enoxaparin (60 mg/day) and aspirin	Symptoms developed despite treatment with aspirin. Treatment was only partially successful, and the patient also developed bleeding
Takasugi et al 2005 [54]	19	M	Afibrinogenemia	-	Numerous thromboses in the mesenteric veins	Infusion of unfractionated heparin: 2,000 unit bolus than 500 U/hr	-	Patient underwent surgical procedures for splenic rupture, intracranial bleeding and mandibular abscess, with prophylactic administration of fibrinogen concentrate, during the year before thrombosis
Al-Mondhiry et al. 1987 [55]	51	F	Dysfibrinogenemia	-	Deep vein thrombosis right thigh and calf; then similar condition on left lower extremity; then thrombosis of left femoral and popliteal veins; then cyanosis of fingers	Heparin and then warfarin for a few months; aspirin and dipyridamole; heparin; flow molecular weight dextran, aspirin, warfarin	Warfarin	Patient was moderately obese and had mild hypertension. Patient also had lupus anticoagulant
Bandyopadhyay et al. 2010 [56]	15	F	Dysfibrinogenemia	-	Portal vein thrombosis	-	-	-
Borrell et al. 1995 [57]	71	M	Dysfibrinogenemia	FGG	Venous thrombosis in right leg	-	-	Thrombotic episode occurred after surgery for ureter lithiasis
Carrell et al. 1983 [58]	11	M	Dysfibrinogenemia	-	History of pulmonary embolism and DVT of lower extremities since age 10	Conservative measures; subsequently, heparin followed by Coumadin for 6 months; then dipyridamole and aspirin	Coumadin anticoagulation	Recurrent episodes of thrombosis that started within a year after getting a deep cut that required 25 sutures. Patient was obese and had moderate hypertension
Castaman et al. 2005 [59]	36	F	Dysfibrinogenemia	FGB	Left iliac-femoral DVT at age 36. Superficial venous thrombosis at 38	First episode: oral anticoagulation (9 months). Second episode: subcutaneous heparin (12,500 U twice daily) for 20 days leading to complete recovery	-	Index case
Castaman et al. 2005 [59]	39	F	Dysfibrinogenemia	FGB	Venous thrombosis of the leg	-	-	Maternal aunt of the index case

Cransac et al. 1995 [60]	57	M	Dysfibrinogenemia	-	Pulmonary embolism, thrombosis of inferior vena cava and several cases of DVT	LMWH (enoxaparine)	Fluindione	Heterozygous protein C deficiency and dysfibrinogenemia, contracted via liver transplantation. The patient received fibrinogen transfusion prior to developing thrombosis
Cransac et al. 1995 [60]	50	F	Dysfibrinogenemia	-	Venous thrombosis of the right leg	Fluindione	-	This patient was the donor of the liver received by the 57-year-old male
Engesser et al. 1988 [61]	45	M	Dysfibrinogenemia	-	Deep leg vein thrombosis	-	-	Occurrence was spontaneous
Fuchs et al. 1977 [62]	20	F	Dysfibrinogenemia	-	Pulmonary embolism and two episodes of deep pelvic thrombosis	Phenprocoumon		Symptoms developed after delivery by caesarean section
Ganti et al. 2007 [21]	36	M	Dysfibrinogenemia	-	Thrombosis initially in superior vena cava and descending thoracic aorta, then in internal jugular vein, then in the descending aorta	Enoxaparin 1.5 mg/kg/day. Then argatroban for a few days and cryoprecipitate to keep fibrinogen level above 200 mg/dL. Then fondaparinux 7.5 mg subcutaneous daily	Fondaparinux	Patient received stem cell transplantation. First episode of thrombosis was before transplant, second episode ~1 month post-transplant. For the transplant, fibrinogen levels were maintained with cryoprecipitate
Hessel et al. 1995 [63]	26	F	Dysfibrinogenemia	-	Pulmonary embolism and recurrent thrombotic episodes since age 26	-	Anticoagulants; subcutaneous heparin during pregnancy	First episode developed 5 days after arthrotomy, but subsequent episodes developed despite treatment with anticoagulants
Jagathesan et al. 2003 [64]	34	M	Dysfibrinogenemia	-	Right axillary deep venous thrombosis	Intravenous heparin, followed by oral anticoagulation with warfarin for 4 months	-	Thrombosis developed after fall from ladder
Kamijyo et al. 2009 [65]	9	M	Dysfibrinogenemia	FGB	MRI revealed infarction of the left medulla oblongata	-	-	-
Kotlin et al. 2009 [66]	26	F	Dysfibrinogenemia	FGG	Pulmonary embolism and DVT in an ileofemoral location; subsequent occurrence of PE (6 years later)	Treated with aspirin and flutamin for a year after initial thrombotic event	-	Patient had no bleeding tendencies

Kotlin et al. 2009 [66]	61	M	Dysfibrinogenemia	FGA	Femoropopliteal DVT in the right leg, as well as ipsilateral superficial thrombophlebitis in calf and contralateral great saphenous vein	-	-	Urgent neurosurgery for subarachnoid bleeding performed 5 weeks before thrombosis
Kotlin et al. 2010 [67]	55	M	Dysfibrinogenemia	FGB	DVT in right calf and pulmonary embolism in right lung	-	-	-
Niwa et al. 2008 [68]	36	F	Dysfibrinogenemia	FGG	DVT in left popliteal and iliac veins and pulmonary embolism	-	-	Thrombosis developed 17 days post-partum
Quattrone et al. 1983 [69]	21	M	Dysfibrinogenemia	-	Complete obstruction of the abdominal aorta	Aorto-bifemoral bypass surgery	-	Patient was a smoker (≤ 5 cigarettes per day)
Quattrone et al. 1983 [69]	26	F	Dysfibrinogenemia	-	Occlusion of internal carotid artery	-	-	-
Reber et al. 1986 [70]	47	F	Dysfibrinogenemia	FGG	DVT and pulmonary embolism; subsequent thromboembolism	-	-	Episodes occurred following interruptions of pregnancies
Robert-Ebadi et al. 2008	5	M	Dysfibrinogenemia	FGG	Left leg iliac thrombosis	Anticoagulant treatment	-	Thrombosis occurred 15 days after surgery for acute appendicitis
Siebenlist et al. 2000 [71]	47	F	Dysfibrinogenemia	FGG	Recurrent episodes of pulmonary embolism and thrombophlebitis	Anticoagulant treatment and vena cava plication	Coumadin anticoagulation	Thrombosis occurred both post-partum and spontaneously. The patient had factor V Leiden mutation
Takala et al. 1991 [42]	28	F	Dysfibrinogenemia	-	Pulmonary embolism; subsequently, suspected DVT in leg and then thrombophlebitis of same leg	Streptokinase and warfarin; subsequently, subcutaneous heparin	Warfarin	Symptoms developed after arthrotomy, and subsequently during pregnancy
Travlou et al. 2010 [72]	43	M	Dysfibrinogenemia	FGG	Myocardial infarction (detected from family history)	-	-	The patient had factor V Leiden mutation
Wada and Lord 1994 [73]	10	M	Dysfibrinogenemia	FGA	Recurrent thrombotic disease, including multiple episodes of pulmonary embolism	-	Oral anticoagulants	Thrombotic episodes despite the patient being on oral anticoagulants
Ingram et al. 1966 [74]	31	F	Fibrinogen deficiency	-	Thrombotic embolus in the artery supplying lower lobe of the right lung (pulmonary embolism)	-	-	Treatment details not clear. Patient underwent hysterectomy 6 months before thrombosis

Ingram et al. 1966 [74]	28	M	Fibrinogen deficiency	-	Deep vein thrombosis in right-calf; post-mortem showed recent infarct involving the outer part of the lower half of the posterior wall and apex of the left ventricle. Microscopic examination showed recent pale infarcts in the lungs (multiple emboli)	-	-	The patient, who was obese, had a large pleural effusion prior to thrombosis. Repeated infusions of blood, fibrinogen and plasma were given to try and stop bleeding into the pleura. The patient's illness, related to the pleural effusion and thrombotic events, led to death
Cheah et al. 2012 [39]	20	M	Hypodysfibrinogenemia	FGG	Extensive thrombus from the splenic hilum to the porta hepatis, with near total obliteration of the portal venous system	Enoxaparin (1 mg/kg twice daily) and warfarin (INR 2.0-3.0)	Indefinite anticoagulation	-
Hamano et al. 2004 [75]	36	M	Hypodysfibrinogenemia	FGG	Thrombi in thoracic and abdominal aorta and superior mesenteric artery. History of pulmonary embolism and other thromboembolic episodes	-	-	-
Ieko et al. 1991 [76]	59	M	Hypodysfibrinogenemia	-	Thrombosis in peroneal and pulmonary arteries; popliteal and ileofemoral systems and deep veins of the legs	-	-	Symptoms developed despite ongoing treatment with anticoagulants for angina
Rea and Hunt 2012 [77]	20	M	Hypodysfibrinogenemia	FGA + FGG	Repeated pulmonary emboli and intra-cardiac thrombosis	Heparin infusion	Warfarin, target INR 2.0-3.0	Patient initially received fibrinogen during surgical removal of pulmonary embolus. Second event occurred 4 months after surgery. Fibrinogen was administered as well as heparin and warfarin after thrombosis. No new events have occurred since
Rea and Hunt 2012 [77]	40	M	Hypodysfibrinogenemia	FGB	Repeated ischemic strokes	Warfarin (target INR 3.0-4.0) with aspirin and pravastatin	Warfarin	Strokes developed despite treatment with warfarin, but no new events have occurred since treatment was augmented with fibrinogen

Wulf et al. 1999 [41]	20	F	Hypodysfibrinogenemia	-	Recurring pulmonary embolism; thrombus in vena cava and popliteal, femoral and iliac veins	Transient vena cava filter placed; intravenous heparin; emergency embolectomy	Phenprocoumon	Patient was a smoker and using oral contraceptives
Brennan et al. 2006 [78]	14	F	Hypofibrinogenemia	FGB + FGG	Thrombotic stroke at age 14	-	-	-
Bukowski et al. 1962 [79]	14	M	Hypofibrinogenemia	-	Arteriolo-capillary thrombosis of the kidney	-	-	Patient was moderately obese
Castaman et al. 2009 [17]	65	F	Hypofibrinogenemia	FGB	Ischemia in left foot. Bilateral thrombotic occlusion of anterior tibial artery	Urokinase 100,000 U bolus, then 100,000 U/h every 12 h plus unfractionated heparin at 900 U/h; iloprost 2 ng/kg/min for 15 days; dalteparin 5,000 U every 12 h for 3 days	Low-dose aspirin (100 mg/day)	-
Chafa et al. 1995 [6]	39	F	Hypofibrinogenemia	-	Ischemic necrosis of several toes and fingers	-	-	Thrombosis developed prior to fibrinogen treatment
de Raucourt et al. 2005 [80]	26	M	Hypofibrinogenemia	FGG	DVT in right leg and pulmonary embolism	-	-	-
Gormsen 1961 [81]	73	M	Hypofibrinogenemia	-	DVT in iliac and femoral veins	Anticoagulant medication	-	Patient underwent surgery for prostate cancer and was treated with fibrinogen (Serum Institute, Copenhagen) shortly before thromboembolic events occurred
Gormsen 1961 [81]	66	M	Hypofibrinogenemia	-	Iliac vein thrombosis and pulmonary embolism	-	-	Patient underwent (pyelolithotomy and nephrostomy as well as inguinal herniotomy) and was treated with fibrinogen (Serum Institute, Copenhagen) shortly before thromboembolic events occurred. Patient died shortly after pulmonary embolism was found

Hanano et al. 1991 [44]	54	F	Hypofibrinogenemia	-	Left atrial thrombosis	Antithrombin III concentrate (1,500 U/day for 3 days) and heparin (10,000 U/day); subsequently, nafamostat mesilate (90 mg/day); subsequently, surgical thrombectomy	-	-
Hanano et al. 1991 [44]	63	F	Hypofibrinogenemia	-	Left atrial thrombosis	Heparin (10,000 U/day); thrombectomy	-	-
Hanano et al. 1991 [44]	58	F	Hypofibrinogenemia	-	Repeated episodes of left retinal vein thrombosis and transient ischemic attack	-	-	-
Lefebvre et al. 2004 [10]	43	M	Hypofibrinogenemia	FGA	Pulmonary emboli; thrombi in femoral veins; subsequently, thrombus in descending aorta and pulmonary embolism; subsequently, femoral arterial clots	Inferior vena cava filter, and anticoagulants for 3 months; subsequently, low molecular weight heparin (subcutaneous)	LMWH and aspirin	Initial thrombosis occurred shortly after surgery (total hip arthroplasty) during which cryoprecipitate was used.
Marchi et al. 2012 [82]	56	F	Hypofibrinogenemia	FGB	Left-sided central retinal artery occlusion and transient cerebral ischemia	-	-	-
Miljic et al. 2015 [83]	25	M	Hypofibrinogenemia	-	Deep vein thrombosis presenting as thrombotic mass in right femoral and popliteal vein	Low molecular weight heparin (80 anti Xa/kg bodyweight twice daily, subcutaneous)	-	The patient had factor V Leiden mutation (congenital thrombophilia)
Nilsson et al. 1966 [84]	36	M	Hypofibrinogenemia	-	Thrombosis of the left leg (two occasions); cyanotic big toe; thrombi in arteries of the ileum; thrombophlebitis of abdominal wall and arms	-	-	Patient underwent appendicitis surgery (before first occurrence of thrombosis); received a blow to the left lower leg (second occurrence); and underwent surgery in response to peritonitis (last occurrence) Patient died 2 days after surgery in response to peritonitis. Fibrinogen (Kabi) was given during operative procedures

Sheen et al. 2006 [85]		F	Hypofibrinogenemia	FGG	Chronic thromboembolic disease	-	-	FFP and cryoprecipitate was administered during dental extractions
Taslimi and Golshani 2011 [86]	27	F	Hypofibrinogenemia	-	Thrombosis of mesenteric and portal veins	Heparin	-	Patient was admitted to hospital with intra-abdominal bleeding and thrombosis. Patient reported prior use of fibrinogen concentrate (1 g/day) without visiting any physician; fibrinogen concentrate administered after admission to maintain plasma level 50-100 mg/dL. Patient died after surgery