Supplementary Material

Online Table 1: molecular results and clinical data for full vEDS cohort. PM=post mortem. *Variants submitted to the Global Variome shared LOVD.

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	22	relative	c.539G>A p.(Gly180Asp)	1	paternally inherited	haemoptysis age 22	0	no	Yes
male	30	proband	c.539G>A p.(Gly180Asp)	1	unknown	arterial events		abdominal haemorrhage age 31	No
female	27	proband	c.547G>A p.(Gly183Ser)	1	de novo	arterial events bowel: sigmoid colon age 9, small bowel age 21	0	renal infarction, infracolic haematoma age 28	Yes
female	28	proband	c.584G>T p.(Gly195Val)	1	paternally inherited	arterial events bowel: large bowel age 29, small bowel age 29	0	no	No
male	29	proband	c.593G>T p.(Gly198Val)	1	unknown	arterial events multiple pneumothorax age 26		no	Yes
female	28	proband	c.610G>C p.(Gly204Arg)	1	unknown	arterial events	1 before	no	Yes
male	10 months	relative	c.610G>C p.(Gly204Arg)	1	maternally inherited	pneumothorax age 1 day		no	No
male	7	proband	c.656G>A p.(Gly219Asp)	1	paternally inherited	no		no	Yes
female	18	proband	c.664G>C p.(Gly222Arg)	1	maternally inherited	no	0	no	Yes
female	27	Relative	c.755G>T p.(Gly252Val)	1	paternally inherited	arterial events	0	no	Yes
female	30	proband	c.755G>T p.(Gly252Val)	1	unknown	arterial events	0	no	Yes
male	33	proband	c.755G>T p.(Gly252Val)	1	paternally inherited	arterial events		no	Yes
male	59	Relative	c.755G>T p.(Gly252Val)	1	maternally inherited	arterial events		no	No
male	13	relative	c.755G>T p.(Gly252Val)	1	paternally inherited	no		no	Yes
male	16	proband	c.755G>T p.(Gly252Val)	1	paternally inherited	bowel rupture: sigmoid colon age 16		no	Yes
male	PM	relative	c.755G>T p.(Gly252Val)	1	unknown	arterial events pneumothorax multiple		arterial dissection age 34	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	38	relative	c.845G>A p.(Gly282Glu)	1	maternally inherited	no	2 before & after	no	Yes
female	56	proband	c.845G>A p.(Gly282Glu)	1	de novo	arterial events	3 before	no	Yes
male	2	relative	c.845G>A p.(Gly282Glu)	1	maternally inherited	no		no	No
female	29	proband	c.899G>A p.(Gly300Asp)	1	paternally inherited	arterial events	0	no	Yes
female	18	proband	c.970G>A p.(Gly324Ser)	1	unknown	arterial events	1 after	no	Yes
male	33	proband	c.970G>A p.(Gly324Ser)	1	paternally inherited	arterial events		no	Yes
female	23	relative	c.998G>A p.(Gly333Asp)	1	paternally inherited	no	0	no	Yes
male	16	relative	c.998G>A p.(Gly333Asp)	1	paternally inherited	pneumothorax x2 age 14 & 15		no	Yes
male	18	relative	c.998G>A p.(Gly333Asp)	1	paternally inherited	arterial events		aortic dissection age 19	Yes
male	PM	proband	c.998G>A p.(Gly333Asp)	1	paternally inherited	arterial events		aortic dissection age 17	No
female	18	proband	c.1007G>A p.(Gly336Asp)	1	paternally inherited	bowel rupture: large bowel age 12, small bowel age 13	0	no	Yes
male	32	relative	c.1007G>A p.(Gly336Asp)	1	maternally inherited	arterial events pneumothorax, bowel perforation age 13, 16, 30		dissecting thoracic aneurysm age 44	No
female	8 months	relative	c.1241G>A p.(Gly414Asp)	1	maternally inherited	no		no	No
female	PM	proband	c.1241G>A p.(Gly414Asp)	1	unknown	arterial events	1 before	aortic dissection 7 days post c-section age 33	No
male	7	relative	c.1258G>A p.(Gly420Ser)	1	paternally inherited	no		no	No
male	20	relative	c.1258G>A p.(Gly420Ser)	1	paternally inherited	no		no	Yes
male	48	proband	c.1258G>A p.(Gly420Ser)	1	paternally inherited	arterial events pneumothorax age 38		no	Yes
male	PM	relative	c.1258G>A p.(Gly420Ser)	1	paternally inherited	arterial events pneumothorax x2		aortic dissection age 43	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
male	31	Proband	c.1295G>T p.(Gly432Val)	1	de novo	arterial events bowel age 22		no	Yes
female	26	proband	c.1330G>A p.(Gly444Arg)	1	paternally inherited	arterial events bowel age 25	2 before	no	Yes
male	17	relative	c.1330G>A p.(Gly444Arg)	1	maternally inherited	bowel rupture: sigmoid colon age 22		no	Yes
female	47	proband	c.1502G>A p.(Gly501Glu)	1	unknown	arterial events	2 before	vessel rupture in abdomen age 51	Yes
female	24	relative	c.1555G>A p.(Gly519Arg)	1	maternally inherited	bowel rupture: sigmoid colon age 23	2 before	no	Yes
female	30	relative	c.1555G>A p.(Gly519Arg)	1	maternally inherited	bowel rupture: sigmoid colon age 29	2 before	no	Yes
female	51	proband	c.1555G>A p.(Gly519Arg)	1	unknown	bowel rupture: sigmoid colon age 45	2 before	no	Yes
male	19	proband	c.1618G>A p.(Gly540Arg)	1	maternally inherited	arterial events		no	Yes
female	46	proband	c.1700G>A p.(Gly567Glu)	1	paternally inherited	arterial events splenectomy age 13, bowel: colon age 13	0	no	Yes
female	26	relative	c.1744G>A p.(Gly582Ser)	1	maternally inherited	no	3 before	no	Yes
female	52	relative	c.1744G>A p.(Gly582Ser)	1	maternally inherited	arterial events	2 before	pancreatic cancer age 55	Yes
male	5	relative	c.1744G>A p.(Gly582Ser)	1	maternally inherited	no		no	No
male	28	proband	c.1763G>A p.(Gly588Asp)	1	unknown	haemoptysis & haemothorax age 24		no	Yes
male	20	proband	c.1915G>A p.(Gly639Arg)	1	de novo	no		no	Yes
female	6	Relative	c.1988G>A p.(Gly663Asp)	1	paternally inherited	no		no	No
male	42	proband	c.1988G>A p.(Gly663Asp)	1	unknown	arterial events		no	Yes
male	33	proband	c.1996G>A p.(Gly666Ser)	1	paternally inherited	arterial events		no	Yes
male	39	proband	c.2032G>C p.(Gly678Arg)	1	maternally inherited	arterial events		no	Yes
female	16	relative	c.2068G>A p.(Gly690Arg)	1	maternally inherited	no	0	no	Yes
female	46	relative	c.2068G>A p.(Gly690Arg)	1	paternally inherited	no	5 before	no	Yes

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	52	relative	c.2068G>A p.(Gly690Arg)	1	paternally inherited	arterial events	3 before	no	Yes
female	55	relative	c.2068G>A p.(Gly690Arg)	1	paternally inherited	arterial events	2 before	no	Yes
male	25	relative	c.2068G>A p.(Gly690Arg)	1	maternally inherited	no		no	Yes
male	PM	proband	c.2068G>A p.(Gly690Arg)	1	unknown	arterial events		dissecting thoracic aortic aneurysm age 57	No
female	PM	relative	c.2105G>T p.(Gly702Val)	1	de novo	arterial events	1 before	dissected iliac artery in childbirth age 30	No
male	12	proband	c.2105G>T p.(Gly702Val)	1	maternally inherited	arterial events		no	Yes
female	53	proband	c.2123G>C p.(Gly708Ala)	1	unknown	arterial events	0	no	Yes
female	38	proband	c.2177G>T p.(Gly726Val)	1	de novo	arterial events	2 before	no	Yes
female	36	proband	c.2177G>T p.(Gly726Val)	1	unknown	arterial events bowel rupture age 36	1 before	no	No
male	8	relative	c.2177G>T p.(Gly726Val)	1	maternally inherited	no		no	Yes
female	43	proband	c.2285G>T p.(Gly762Val)	1	unknown	arterial events bowel: descending colon age 19 & large bowel age 20	0	no	Yes
female	49	Relative	c.2329G>C p.(Gly777Arg)	1	unknown	no	1 before	no	Yes
female	40	relative	c.2329G>C p.(Gly777Arg)	1	paternally inherited	no	3 before	no	Yes
female	41	relative	c.2329G>C p.(Gly777Arg)	1	paternally inherited	arterial events	2 before	no	Yes
female	34	relative	c.2329G>C p.(Gly777Arg)	1	paternally inherited	no	4 before	no	Yes
female	36	relative	c.2329G>C p.(Gly777Arg)	1	paternally inherited	no	4 before	no	Yes
female	7	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no		no	No
female	13	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no		no	Yes
female	22	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no	0	no	Yes
female	1	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no		no	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
male	22	proband	c.2329G>C p.(Gly777Arg)	1	maternally inherited	arterial events pneumothorax age 25		no	Yes
male	14	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no		no	Yes
male	10	relative	c.2329G>C p.(Gly777Arg)	1	maternally inherited	no		no	No
male	62	proband	c.2329G>C p.(Gly777Arg)	1	inherited - unsure which parent	arterial events		no	Yes
female	3	relative	c.2339G>A p.(Gly780Asp)	1	maternally inherited	no		no	No
female	29	relative	c.2339G>A p.(Gly780Asp)	1	maternally inherited	no	2 before	no	Yes
female	19	relative	c.2356G>A p.(Gly786Arg)	1	maternally inherited	no	0	no	Yes
female	52	proband	c.2356G>A p.(Gly786Arg)	1	paternally inherited	arterial events (diverticulae perforation age 54)	4 before	no	Yes
female	25	relative	c.2356G>A p.(Gly786Arg)	1	maternally inherited	no	0	no	Yes
male	4	relative	c.2356G>A p.(Gly786Arg)	1	paternally inherited	no		no	No
male	9	relative	c.2356G>A p.(Gly786Arg)	1	paternally inherited	no		no	No
male	40	relative	c.2356G>A p.(Gly786Arg)	1	maternally inherited	no		no	Yes
female	50	relative	c.2401G>C p.(Gly801Arg)	1	maternally inherited	bowel rupture age 31 (surgical bowel perforation age 40)	1 before	no	Yes
female	74	relative	c.2401G>C p.(Gly801Arg)	1	unknown	no	1 before	no	No
male	22	proband	c.2401G>C p.(Gly801Arg)	1	maternally inherited	bowel rupture age 16		no	Yes
female	2	proband	c.2483G>A p.(Gly828Glu)	1	paternally inherited	no		no	No
male	42	proband	c.2491G>C p.(Gly831Arg)	1	paternally inherited	haemoptysis age 37		no	Yes
female	11	Relative	c.2554G>T p.(Gly852Cys)	1	paternally inherited	no	0	no	Yes
male	37	proband	c.2554G>T p.(Gly852Cys)	1	paternally inherited	arterial events		no	Yes
male	PM	proband	c.2798G>A p.(Gly933Glu)	1	unknown	arterial events		ruptured vena cava age 15	No
female	22	Relative	c.2834G>A p.(Gly945Asp)	1	maternally inherited	no	0	no	Yes
female	24	Relative	c.2834G>A p.(Gly945Asp)	1	maternally inherited	no	0	no	Yes

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	PM	Relative	c.2834G>A p.(Gly945Asp)	1	unknown	arterial events	4 before	died during heart valve surgery age 39	No
male	PM	proband	c.2834G>A p.(Gly945Asp)	1	maternally inherited	arterial events		coronary artery rupture age 24	No
female	62	relative	c.2851G>A p.Gly951Arg	1	unknown	arterial events	3 before	no	Yes
male	2	relative	c.2851G>A p.Gly951Arg	1	paternally inherited	no		no	No
male	31	relative	c.2851G>A p.Gly951Arg	1	maternally inherited	no		no	Yes
male	PM	proband	c.2851G>A p.Gly951Arg	1	maternally inherited	arterial events		ruptured renal artery age 34	No
male	23	proband	c.2923G>A p.(Gly975Ser)	1	maternally inherited	arterial events		severe retroperitoneal bleeding age 24	Yes
male	12	proband	c.2924G>T p.(Gly975Val)	1	de novo	arterial events		aortic dissection age 20	Yes
female	46	proband	c.2951G>T p.(Gly984Val)	1	unknown	arterial events	2 before	no	Yes
female	38	proband	c.3004G>A p.(Gly1002Ser)	1	paternally inherited	arterial events bowel rupture age 25	4 before	no	Yes
female	28	relative	c.3004G>A p.(Gly1002Ser)	1	paternally inherited	no	0	no	Yes
male	PM	relative	c.3004G>A p.(Gly1002Ser)	1	unknown	arterial events		aortic dissection age 64	No
female	20	Relative	c.3067G>C p.(Gly1023Arg)	1	maternally inherited	haemoptysis age 23	2 before	no	Yes
female	51	Relative	c.3067G>C p.(Gly1023Arg)	1	paternally inherited	arterial events	1 before	no	Yes
female	46	proband	c.3067G>C p.(Gly1023Arg)	1	paternally inherited	arterial events	2 before	no	Yes
male	PM	relative	c.3067G>C p.(Gly1023Arg)	1	maternally inherited	no		seizures secondary to frontal lobe infarction age 19	No
male	4 months	relative	c.3067G>C p.(Gly1023Arg)	1	maternally inherited	no		no	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	26	proband	c.3104G>T p.(Gly1035Val)	1	inherited - unsure which parent	arterial events bowel rupture age 15	1 after	dissection of thoracic aorta age 31	Yes
male	1	Relative	c.3104G>T p.(Gly1035Val)	1	paternally inherited	no		no	No
male	25	Relative	c.3104G>T p.(Gly1035Val)	1	inherited - unsure which parent	arterial events		ruptured thoracic aorta age 29	Yes
female	59	Relative	c.3149G>A p.(Gly1050Asp)	1	unknown	arterial events	3 before	no	Yes
female	PM	proband	c.3149G>A p.(Gly1050Asp)	1	maternally inherited	arterial events	1 before	aortic dissection age 34	No
male	2	Relative	c.3149G>A p.(Gly1050Asp)	1	maternally inherited	no		no	No
female	43	proband	c.3212G>T p.(Gly1071Val)	1	unknown	arterial events haemoptysis - multiple episodes age 44	0	no	Yes
male	2	proband	c.3284G>A p.(Gly1095Asp)	1	de novo	no		no	No
female	67	relative	c.3391G>A p.(Gly1131Ser)	1	inherited - unsure which parent	no	1 before	no	Yes
female	13	relative	c.3391G>A p.(Gly1131Ser)	1	paternally inherited	no		no	Yes
female	63	relative	c.3391G>A p.(Gly1131Ser)	1	inherited - unsure which parent	no	4 before	no	Yes
male	45	relative	c.3391G>A p.(Gly1131Ser)	1	maternally inherited	no		no	Yes
male	64	relative	c.3391G>A p.(Gly1131Ser)	1	inherited - unsure which parent	no		no	Yes
male	11	proband	c.3500G>A p.(Gly1167Asp)	1	paternally inherited	no		no	No
male	38	relative	c.3500G>A p.(Gly1167Asp)	1	unknown	no		no	Yes
male	6	proband	c.3554G>T p.(Gly1185Val)	1	de novo	pneumothorax age 12 weeks		no	Yes
female	27	relative	c.537_554del p.(Pro181_Gly186del)	2	unknown	no	3 before	no	Yes
male	11	proband	c.582+1G>A p.(?)	2	maternally inherited	no		no	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	PM	relative	c.690+1G>A p.(?)	2	unknown	arterial events spleen rupture age 27	2 before	abdominal haemorrhage age 30	No
male	8	relative	c.690+1G>A p.(?)	2	paternally inherited	no		no	No
male	12	relative	c.690+1G>A p.(?)	2	paternally inherited	no		no	No
male	33	proband	c.690+1G>A p.(?)	2	maternally inherited	arterial events		no	Yes
male	PM	relative	c.690+1G>A p.(?)	2	maternally inherited	arterial events spleen rupture age 12, bowel: sigmoid colon age 35		ruptured right renal artery aneurysm age 38	No
female	53	proband	c.952-1G>T p.(?)	2	paternally inherited	no	2 before	no	Yes
female	28	proband	c.996+5G>A p.(?)	2	maternally inherited	no	0	no	Yes
female	47	proband	c.996+5G>A p.(?)	2	de novo	arterial events	3 before	no	Yes
female	40	proband	c.1347+1G>A p.(?)	2	maternally inherited	arterial events	1 before	no	Yes
female	37	proband	c.1662+1G>A p.(?)	2	unknown	arterial events bowel rupture age 22	1 diagnosis made during pregnancy	no	Yes
female	9	proband	c.1662+1G>C p.(?)	2	paternally inherited	no	0	no	Yes
female	3	proband	c.1662+1G>A p.(?)	2	de novo	no		no	No
female	11	proband	c.1662+1G>A p.(?)	2	unknown	bowel rupture: rectum age 11, colon age 12	0	no	Yes
male	20	proband	c.1662+1G>A p.(?)	2	unknown	pneumothorax age 22		no	Yes
female	30	proband	c.1761+5G>A p.(?)	2	de novo	arterial events	0	no	Yes
female	3	relative	c.1761+1G>A p.(?)	2	maternally inherited	no		no	No
female	37	proband	c.1761+1G>A p.(?)	2	maternally inherited	arterial events	1 before	no	Yes
female	15	proband	c.2230-3_2255del p.(?)	2	de novo	arterial events	0	aortic dissection age 19	Yes
male	57	proband	c.2392-2A>G p.(?)	2	inherited - unsure which parent	arterial events		no	Yes
male	5	proband	c.2445+3_2445+6del p.(?)	2	de novo	no		no	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
male	16	proband	c.3039+3G>C p.(?)	2	de novo	bowel rupture age 16		no	Yes
female	22	relative	c.3201+1G>C p.(?)	2	unknown	no	1 before	no	Yes
male	prenatal	proband	c.3201+1G>C p.(?)	2	maternally inherited	no		no	No
female	50	relative	c.3213_3221dup p.(Pro1072_Gly1074dup)	2	unknown	arterial events	2 before	no	Yes
female	38	proband	c.3525+1G>A p.(?)	2	unknown	no	0	no	Yes
male	18	proband	c.3525+2T>C p.(?)	2	unknown	no		no	Yes
male	15	proband	c.3823+1G>A p.(?)	2	de novo	no		no	Yes
female	4	proband	c.20022+2T>C p.(?)	2	de novo	no	0	no	Yes
female	17	Relative	c.382C>T p.(Gln128*)	3	paternally inherited	no	0	no	Yes
male	51	proband	c.382C>T p.(Gln128*)	3	inherited - unsure which parent	arterial events		no	Yes
female	73	Relative	c.592G>T p.(Gly198*)	3	unknown	no	2 before	lung cancer age 76	Yes
male	38	proband	c.592G>T p.(Gly198*)	3	maternally inherited	arterial events		no	Yes
male	6	relative	c.592G>T p.(Gly198*)	3	paternally inherited	no		no	No
male	47	proband	c.1714C>T p.(Arg572*)	3	paternally inherited	arterial events		no	Yes
female	44	proband	c.1979delG p.(Gly660Valfs*131)	3	maternally inherited	no	2 before	no	Yes
male	22	relative	c.1979delG p.(Gly660Valfs*131)	3	maternally inherited	no		no	Yes
female	27	proband	c.2409_2422del14 p.(Gly804Cysfs*12)	3	inherited - unsure which parent	arterial events	1 after	no	Yes
male	28	Relative	c.2409_2422del14 p.(Gly804Cysfs*12)	3	inherited - unsure which parent	arterial events Spleen rupture age 22		no	Yes
female	20	relative	c.2797G>T p.(Gly933*)	3	paternally inherited	no	0	no	Yes
male	17	proband	c.2797G>T p.(Gly933*)	3	paternally inherited	arterial events		no	Yes
male	PM	relative	c.2797G>T p.(Gly933*)	3	maternally inherited	arterial events		aortic dissection age 44	No

Sex	Age at diagnosis	Proband/ Relative	Molecular result*	Variant Group	Inheritance	vEDS related events	Pregnancy before/ after diagnosis	Deceased	In statistical analysis cohort
female	52	proband	c.4138delG p.(Asp1380Ilefs*7)	3	unknown	bowel rupture: sigmoid colon age 46	4 before	no	Yes
male	17	Relative	c.4294C>T p.(Arg1432*)	3	paternally inherited	no		no	Yes
male	PM	proband	c.4294C>T p.(Arg1432*)	3	maternally inherited	arterial events		dissecting aortic aneurysm age 55	No
female	22	proband	c.4400A>T p.(Leu1467*)	3	de novo	no	1 after	no	Yes
female	8	proband	2q deletion including *COL3A1*	3	de novo	no		no	No
female	prenatal	proband	2q deletion including *COL3A1*	3	de novo	no		no	No
female	6	proband	2q deletion including *COL3A1*	3	de novo	no		no	No
female	1	proband	2q deletion including *COL3A1*	3	de novo	no		no	No

Online Table 2: Clinical Arterial score (CA score)

Definition of the clinical arterial score and illustrations of patient staging from Frank et al., 2019 [10].

- 0 point: no clinical arterial event
- 1 point: a silent dissection; an aneurysm; a false aneurysm
- 2 points: a symptomatic dissection
- 5 points: an arterio-venous fistula; a lower or upper limb arterial rupture
- 10 points: a carotid-cavernous fistula; an aortic dissection and/or rupture; an abdominal artery rupture; an intrathoracic artery rupture

Points were assigned according to expected clinical consequences of each arterial type of lesion, the highest points being assigned to life-threatening arterial accidents. The arterial score can only increase throughout follow-up and boundaries were chosen to allow easy group changes, particularly for life-threatening accidents.

Group 1 (very low, score 0-1 point)	• No clinical arterial event (0 point) • A silent dissection (1 point) • An aneurysm (1 point) • A false aneurysm (1 point)
Group 2 (low, score 2-8 points)	• A symptomatic dissection (2 points) • A symptomatic dissection (2 points) and an aneurysm (1 point) (=3 points) • An arterio-venous fistula (5 points) and a symptomatic dissection (2 points) (=7 points) • A lower or upper limb arterial rupture (5 points) and a symptomatic dissection (2 points) and a silent dissection (1 point) (=8 points)
Group 3 (medium, score 9-19 points)	• An arterio-venous fistula (5 points), a symptomatic dissection (2 points) and 2 silent dissections (2 points) (=9 points) • A carotid-cavernous fistula (10 points) • An aortic rupture (10 points) and a lower or upper limb arterial rupture (5 points) (=15 points) • An intracranial artery rupture (10 points), an arteriovenous fistula (5 points), and 2 symptomatic dissections (4 points) (=19 points)
Group 4 (high, score ≥20 points)	• An abdominal artery rupture (10 points) and an intrathoracic artery rupture (10 points) (=20 points) • A carotid-cavernous fistula (10 points), 5 symptomatic dissections (10 points), and 3 aneurysms (3 points) (=23 points) • An aortic rupture (10 points), 2 lower or upper limb arterial ruptures (10 points), and 3 symptomatic dissections (6 points) (=26 points) • Two abdominal artery ruptures (20 points), a lower or upper limb arterial rupture (5 points), and 2 symptomatic dissections (4 points) (=29 points)

Online Table 3: Characteristics of those who died before being seen by the service

Sex	Diagnosed vEDS	vEDS variant	Inherited?	Age deceased	Cause of death
Male	PM COL3A1 FDR	Group_III	Yes	44	aortic dissection
Male	PM COL3A1 OC	Group_I	unknown	64	aortic dissection
Male	COL3A1 result PM	Group_I	unknown	15	ruptured vena cava
Female	Clinical diagnosis PM, COL3A1 FDR	Group_I	No	30	dissected iliac artery in childbirth
Male	COL3A1 result PM	Group_I	Yes	19	seizures secondary to frontal lobe infarction
Female	COL3A1 result PM	Group_I	Yes	35	aortic dissection
Female	COL3A1 result PM	Group_I	unknown	33	aortic dissection 7 days post c-section
Male	PM COL3A1 OC	Group_I	Yes	34	ruptured renal artery
Male	COL3A1 result PM	Group_III	Yes	55	dissecting aortic aneurysm
Male	Clinical diagnosis COL3A1 OC	Group_I	Yes	44	dissecting thoracic aneurysm
Male	COL3A1 result PM	Group_I	Yes	24	coronary artery rupture
Female	COL3A1 result PM	Group_I	unknown	40	died during heart valve surgery
Male	PM COL3A1 OC	Group_I	unknown	34	right common iliac arterial dissection
Male	COL3A1 result PM	Group_I	Yes	18	Dissection of whole length of aorta
Male	PM COL3A1 OC	Group_II	Yes	37	ruptured right renal artery aneurysm
Female	Clinical diagnosis COL3A1 in FDR	Group_II	unknown	30	abdominal hemorrhage
Male	PM COL3A1 OC	Group_I	unknown	57	dissecting thoracic aortic aneurysm
Male	COL3A1 test, result reported PM	Group_I	unknown	31	bleed into abdomen
Male	PM COL3A1 OC	Group_I	Yes	43	aortic dissection

PM=post mortem diagnosis, OC=obligate carrier given results in the family, FDR=result in first degree relative

Online Table 4: showing *COL3A1* inheritance for probands and relatives

inherited_dum	Index case or relative: Relative	Index	Total
unknown	8	18	26
	14.29	25.71	20.63
No	0	14	14
	0.00	20.00	11.11
Yes	48	38	86
	85.71	54.29	68.25
Total	56	70	126
	100.00	100.00	100.00

Online Table 5: transitions in treatment from baseline to end of study

Key

frequency
row percentage

basetreat	endtreat: ARB	BB	BB&ARB	celi	celi&ARB	no treatm	Total
ARB	0	0	2	0	0	0	2
	0.00	0.00	100.00	0.00	0.00	0.00	100.00
BB	0	0	6	0	0	0	6
	0.00	0.00	100.00	0.00	0.00	0.00	100.00
BB&ARB	0	0	6	0	0	0	6
	0.00	0.00	100.00	0.00	0.00	0.00	100.00
celi	1	0	3	2	8	0	14
	7.14	0.00	21.43	14.29	57.14	0.00	100.00
no treatm	17	9	56	0	1	15	98
	17.35	9.18	57.14	0.00	1.02	15.31	100.00
Total	18	9	73	2	9	15	126
	14.29	7.14	57.94	1.59	7.14	11.90	100.00

Online Table 6: Evolution of the arterial score

RECODE of fscore (fscore)	FSprogendFU				
	very low	low	medium	high	Total
very low	78	3	7	0	88
	88.64	3.41	7.95	0.00	100.00
low	0	23	3	0	26
	0.00	88.46	11.54	0.00	100.00
medium	0	0	9	2	11
	0.00	0.00	81.82	18.18	100.00
high	0	0	0	1	1
	0.00	0.00	0.00	100.00	100.00
Total	78	26	19	3	126
	61.90	20.63	15.08	2.38	100.00

Online Table 7: Evolution of the arterial score by treatment at end of follow up

Treatment: ARB

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	low	medium	Total
very low	14 93.33	0 0.00	1 6.67	15 100.00
low	0 0.00	3 100.00	0 0.00	3 100.00
Total	14 77.78	3 16.67	1 5.56	18 100.00

Treatment: BB

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	low	Total
very low	7 87.50	1 12.50	8 100.00
low	0 0.00	1 100.00	1 100.00
Total	7 77.78	2 22.22	9 100.00

Treatment: BB&ARB

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	low	medium	high	Total
very low	43 91.49	2 4.26	2 4.26	0 0.00	47 100.00
low	0 0.00	15 93.75	1 6.25	0 0.00	16 100.00
medium	0 0.00	0 0.00	8 88.89	1 11.11	9 100.00
high	0 0.00	0 0.00	0 0.00	1 100.00	1 100.00
Total	43 58.90	17 23.29	11 15.07	2 2.74	73 100.00

Treatment: celi

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	medium	Total
very low	1 50.00	1 50.00	2 100.00
Total	1 50.00	1 50.00	2 100.00

Treatment: celi&ARB

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	low	medium	Total
very low	4 100.00	0 0.00	0 0.00	4 100.00
low	0 0.00	3 75.00	1 25.00	4 100.00
medium	0 0.00	0 0.00	1 100.00	1 100.00
Total	4 44.44	3 33.33	2 22.22	9 100.00

Treatment: no treatm

Key
frequency *row percentage*

RECODE of fscore (fscore)	FSprogendFU very low	low	medium	high	Total
very low	9 75.00	0 0.00	3 25.00	0 0.00	12 100.00
low	0 0.00	1 50.00	1 50.00	0 0.00	2 100.00
medium	0 0.00	0 0.00	0 0.00	1 100.00	1 100.00
Total	9 60.00	1 6.67	4 26.67	1 6.67	15 100.00

Online Table 8: Characteristics of patients who died compared to surviving patients.

Characteristics	Alive	Deceased*	p-value
n	116	8	
Sex			0.71
Female	71(61.21)	4(50)	
Male	45(38.79)	4(50)	
Age at start of FU	33(20,45)	24(16,26.75)	0.07
Age at end of FU	37(25,50)	26(19.25,30.5)	0.05
Status			0.46
Relative	52(44.83)	2(25)	
Proband	64(55.17)	6(75)	
Type of variant			0.85
Group I	83(71.55)	7(87.5)	
Group II	20(17.24)	1(12.5)	
Group III	13(11.21)	0(0)	

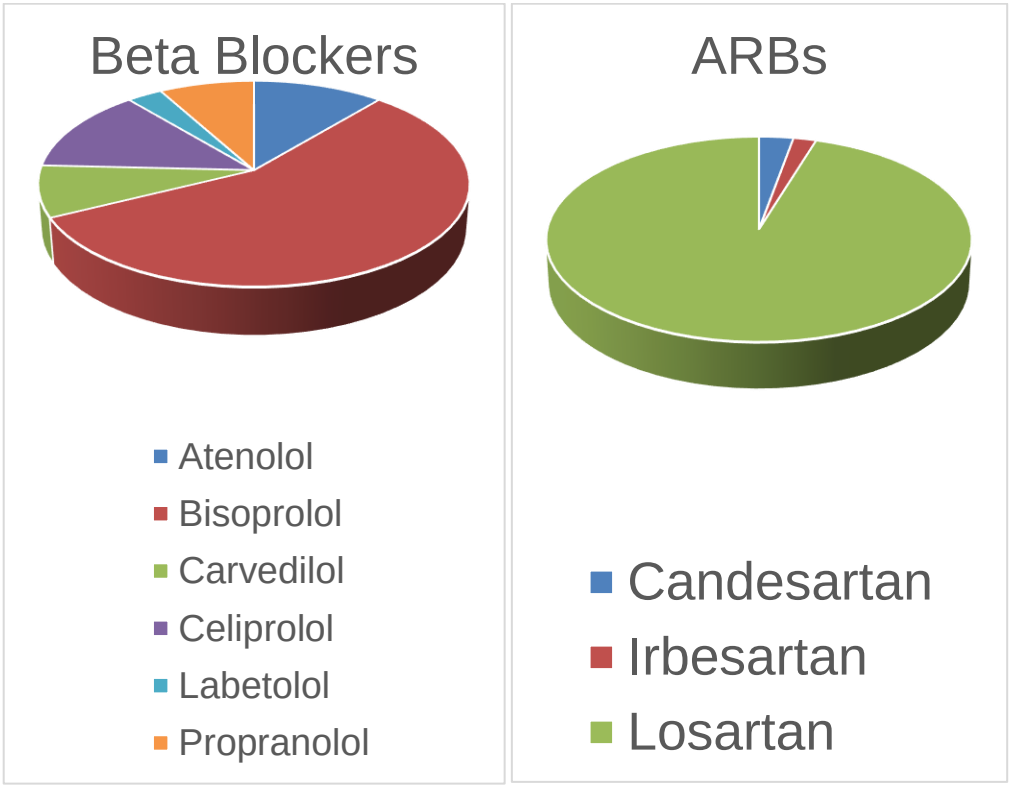
Note: Values are n(%) or median (interquartile range). Fisher exact test for qualitative variables and Kruskal-Wallis test for quantitative variables.
*Excludes two patients who died of vEDS unrelated causes

Online Table 9: Distribution of vascular events in vEDS patients in full cohort.

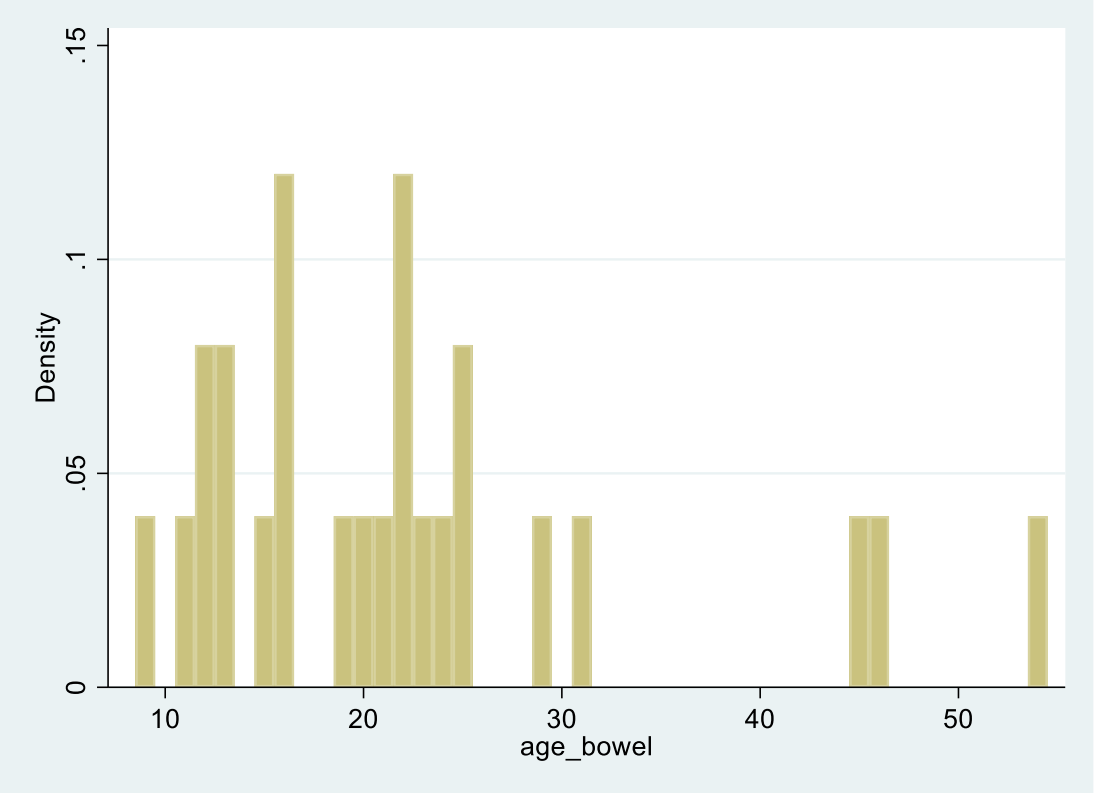
Type and location of vascular events	Number of vascular events	Number of patients
All vascular events	165	72 (40%)
	9	1
	7	2
	6	1
	5	4
	4	5
	3	9
	2	14
	1	36
Dissections	75 (45.45%)	49 (27.22%) (age range 13 to 65 years)
aortic	12	
arm	2	
carotid	13	
coeliac	3	
coronary	7	
femoral	3	
gastrointestinal	2	
hepatic	1	
iliac	18	
leg	1	
renal	7	
splenic	1	
thoracic aorta	4	
vertebral	1	
Ruptures	22 (13.33%)	17 (9.44%) (age range 12 to 51 years)
arm	3	
cerebral	1	
coronary	2	
gastrointestinal	5	
iliac	1	
leg	1	
rectus sheath	2	
renal	3	
splenic	2	
superior vena cava	1	
thoracic aorta	1	
Aneurysms	61 (36.96%)	28 (15.55%) (age range 17 to 63 years)
aortic	2	
arm	3	
carotid	6	
cavernous carotid	1	
cerebral	1	
coeliac	8	
coronary	2	
femoral	3	
gastrointestinal	3	
hepatic	3	
iliac	9	
leg	2	
renal	9	
splenic	6	
thoracic aorta	1	
vertebral	2	
Carotid cavernous fistula	6 (3.63%)	6 (3.33%) (age range 29 to 55 years)
Arteriovenous fistula	1 (0.60%)	1 (0.55%) (age 43 years)

Online Figure 1: image of UK NHS vEDS emergency information card for medical professionals.

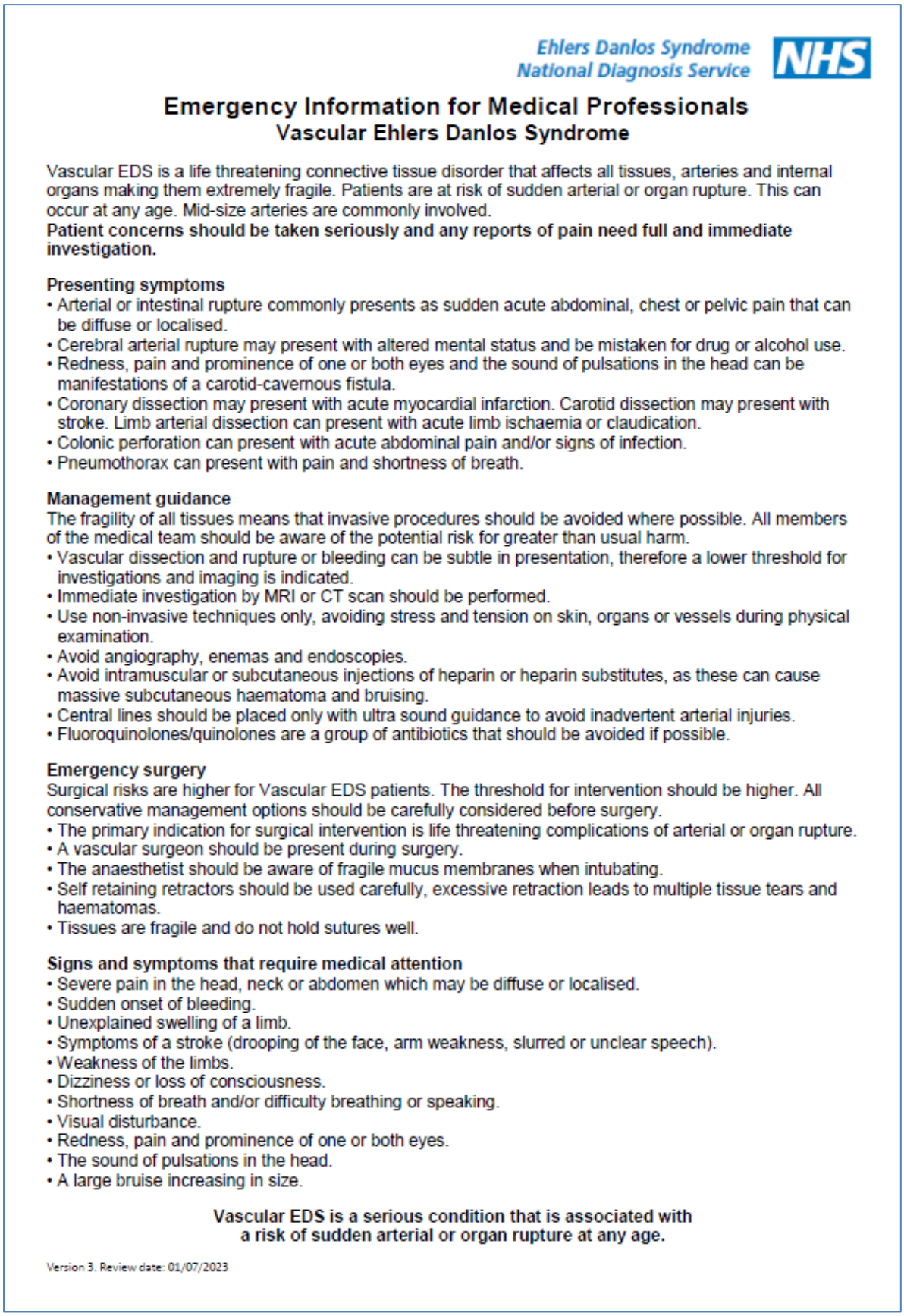
Online Figure 2. Showing range and distribution of BB and ARB used by cohort.



Online Figure 3: Showing peak ages for bowel perforation



Online Figure 4. UK National Diagnostic Service Vascular EDS Emergency Information for Medical Professionals.



Ehlers Danlos Syndrome
National Diagnosis Service
NHS

Emergency Information for Medical Professionals
Vascular Ehlers Danlos Syndrome

Vascular EDS is a life threatening connective tissue disorder that affects all tissues, arteries and internal organs making them extremely fragile. Patients are at risk of sudden arterial or organ rupture. This can occur at any age. Mid-size arteries are commonly involved.
Patient concerns should be taken seriously and any reports of pain need full and immediate investigation.

Presenting symptoms
- Arterial or intestinal rupture commonly presents as sudden acute abdominal, chest or pelvic pain that can be diffuse or localised.
- Cerebral arterial rupture may present with altered mental status and be mistaken for drug or alcohol use.
- Redness, pain and prominence of one or both eyes and the sound of pulsations in the head can be manifestations of a carotid-cavernous fistula.
- Coronary dissection may present with acute myocardial infarction. Carotid dissection may present with stroke. Limb arterial dissection can present with acute limb ischaemia or claudication.
- Colonic perforation can present with acute abdominal pain and/or signs of infection.
- Pneumothorax can present with pain and shortness of breath.

Management guidance
The fragility of all tissues means that invasive procedures should be avoided where possible. All members of the medical team should be aware of the potential risk for greater than usual harm.
- Vascular dissection and rupture or bleeding can be subtle in presentation, therefore a lower threshold for investigations and imaging is indicated.
- Immediate investigation by MRI or CT scan should be performed.
- Use non-invasive techniques only, avoiding stress and tension on skin, organs or vessels during physical examination.
- Avoid angiography, enemas and endoscopies.
- Avoid intramuscular or subcutaneous injections of heparin or heparin substitutes, as these can cause massive subcutaneous haematoma and bruising.
- Central lines should be placed only with ultra sound guidance to avoid inadvertent arterial injuries.
- Fluoroquinolones/quinolones are a group of antibiotics that should be avoided if possible.

Emergency surgery
Surgical risks are higher for Vascular EDS patients. The threshold for intervention should be higher. All conservative management options should be carefully considered before surgery.
- The primary indication for surgical intervention is life threatening complications of arterial or organ rupture.
- A vascular surgeon should be present during surgery.
- The anaesthetist should be aware of fragile mucus membranes when intubating.
- Self retaining retractors should be used carefully, excessive retraction leads to multiple tissue tears and haematomas.
- Tissues are fragile and do not hold sutures well.

Signs and symptoms that require medical attention
- Severe pain in the head, neck or abdomen which may be diffuse or localised.
- Sudden onset of bleeding.
- Unexplained swelling of a limb.
- Symptoms of a stroke (drooping of the face, arm weakness, slurred or unclear speech).
- Weakness of the limbs.
- Dizziness or loss of consciousness.
- Shortness of breath and/or difficulty breathing or speaking.
- Visual disturbance.
- Redness, pain and prominence of one or both eyes.
- The sound of pulsations in the head.
- A large bruise increasing in size.

Vascular EDS is a serious condition that is associated with a risk of sudden arterial or organ rupture at any age.

Version 3. Review date: 01/07/2023

Online Figure 5. Poster Abstract 38, International Scientific Symposium on EDS & HSD, 2022

NHS
Ehlers Danlos Syndrome
National Diagnostic Service

38

Vascular EDS and Pregnancy

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Background

The UK EDS Diagnostic service was established in 2009 to improve diagnosis for people with the rare types of EDS. The service has two clinic locations; Sheffield and London. Over 200 patients diagnosed with vascular EDS (vEDS) have now been seen by the team in Sheffield. The service has been involved in the care of women whose diagnosis of vEDS has been made during pregnancy, before pregnancy and women who had pregnancies before knowing their diagnosis.

Discussion with patient

We talk to our patients about the risks associated with pregnancy for women with vEDS as well as the 50% chance of a child inheriting the condition if either parent has the diagnosis. We discuss reproductive options, including prenatal diagnoses, preimplantation genetic testing (PGT), surrogacy and adoption with both male and female patients who may be considering a family. We give specific advice on the associated risk of each option for women with vascular EDS. Pregnancy is known to carry significant risks for women with vEDS (1). All women with vEDS are classified as high-risk in terms of pregnancy management (2) and need carefully coordinated care under specialist obstetric services in tertiary care. Prior history of vascular events of hollow organ rupture would further increase these risks.

Reproductive options

- Antenatal diagnosis by chorionic villus sampling (CVS) between 11-14 weeks of pregnancy or amniocentesis between 15-20 weeks of pregnancy may be considered by women with vEDS. These procedures carry a risk of miscarriage for all women (up to 1%). Additional risks for women with vEDS are unknown but expected given the increased tissue fragility. The timing of the procedure should be considered, with the option of admitting the patient, rather than managing as an outpatient.
- Termination of pregnancy may be considered by women with vEDS. The additional risks of termination of pregnancy for women with vEDS are unknown. Medical termination would be advised rather than surgical termination due to blood vessel and tissue fragility and bleeding risks.
- Egg donation with surrogacy may be considered by women with vEDS not wanting the risks associated with carrying a pregnancy. For women choosing to use their own egg the additional risks for women with vEDS related to ovarian hyperstimulation and egg retrieval are unknown.
- Preimplantation genetic testing (PGT) may be considered by women with vEDS and may be offered depending on medical history. Additional risks for women with vEDS are unknown but include potential risks from ovarian hyperstimulation and egg retrieval, as well as risks associated with pregnancy.
- Adoption/Fostering may be considered by women with vEDS to avoid the risks associated with pregnancy. A welfare of the child assessment will include consideration of the woman's vEDS diagnosis and statements from specialists involved are likely to be requested.

Prior to pregnancy

Beta-blockers and Losartan are often used in the management of vEDS. Losartan is contraindicated in pregnancy, this should be stopped, ideally before pregnancy. Beta-blockers may need to be changed (to alternative beta blocker labetalol) during pregnancy. Beta-blockers carry a small risk of fetal growth restriction so serial fetal growth scans should be arranged.

Where possible, MRA scans should be performed prior to pregnancy and should be reviewed with plans for further imaging based on these results. Scans in pregnancy may be needed if no previous scans are available. Postpartum vascular imaging is recommended at 3 months.

Pregnancy timeline

Pregnancy management for women with vEDS

The Sheffield EDS Diagnostic Service have now been involved with the successfully delivery of 12 babies to women with known diagnosis of vEDS. These pregnancies were closely managed by a specialist obstetric team in a tertiary unit with MDT involvement including; obstetrics, anaesthetists, vascular surgeons, clinical genetics, cardiology (including cardiologist with special knowledge of vEDS) and input from the EDS Diagnostic Service.

Early elective caesarean section with delivery suggested at 34/35 weeks to balance the risks to the baby of early delivery with the risks of spontaneous labour for the mother. There is an increased risk of premature birth for babies with vEDS and an increased risk of PROM for mothers with vEDS. Antenatal steroid administration for fetal lung maturation is recommended between 24 hours and 7 days prior to delivery.

An obstetric anaesthetic assessment should take place in the antenatal period. A specialist obstetric anaesthetist is required for delivery and the method of anaesthesia needs to be carefully considered. A vascular surgeon (and appropriate surgical equipment) should be available in theatre for immediate expert repair of vessels if needed. Protocolised management of Massive Obstetric Haemorrhage (MOH) should be readily accessible for those patients that bleed; ideally, as well as cross-matched blood, use of cell salvage, bedside monitoring of clotting function (to guide blood product administration), and fibrinogen concentrate.

Parents may wish to have cord blood stored at birth to allow genetic testing at a later date. It is helpful to have a request form completed for the parents to hand over before delivery.

Some women with vEDS may wish to consider the option of having a tubal ligation at the time of delivery. Other contraceptive options can be discussed. Although it is possible to fit a coil under direct vision at c-section, replacement carries risk as it is not performed under direct vision and there is an increased risk of uterine perforation or coil migration

Mother – to be observed in obstetric HDU or critical care unit overnight with critical care team aware. Consider extending the postnatal stay in hospital as vessel dissection and rupture in the mother are reported also in the postnatal period.

Pregnancy management for partners of men with vEDS

Men with vEDS have the same reproductive options as women. There is a 50% chance of a baby inheriting vEDS and in the absence of genetic testing the potential for preterm delivery should be recognised. Parents may wish to have cord blood stored at birth to allow genetic testing at a later date. It is helpful to have a request form completed for the parents to hand over before delivery

Neonate at 50% risk of having vEDS

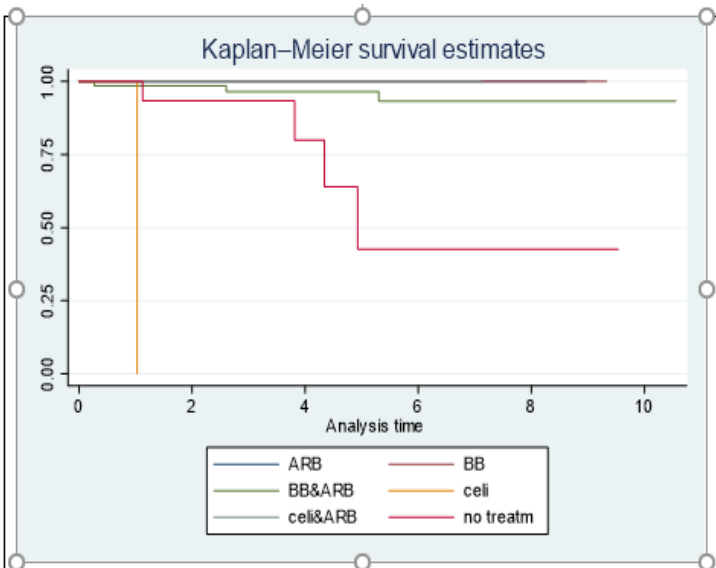
The neonatal team needs to be aware of the risk of vEDS in the baby and potential complications in an affected neonate. It is not possible to make a confident clinical diagnosis of vEDS in a neonate. Talipes is seen more commonly in babies with vEDS. There are cases of pneumothorax reported in the early neonatal period if the baby is affected with vEDS.

There are currently no international guidelines for the management of pregnancy for women with vEDS. By sharing our experience of successfully managed pregnancies and deliveries we hope to be able to improve the outcomes for women with vEDS in pregnancy.

References:
1) MURRAY, M.L., PEPIN, M., PETERSON, S. and BYERS, P.H., 2014. Pregnancy-related deaths and complications in women with vascular Ehlers–Danlos syndrome. *Genetics in medicine*, **16**(12), pp. 874-880.
2) 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European Heart Journal (2018) 39, 3165–3241

Online Figure 6: Additional survival curves

a) All treatment groups: log=rank test for equality of survivor functions. p-value =0.00



By treatment group: log=rank test for equality of survivor functions
p-value =0.00

Equality of survivor functions
Log-rank test

endtreat	Observed events	Expected events
ARB	0	0.86
BB	0	0.59
BB&ARB	3	5.31
celi	1	0.03
celi&ARB	0	0.40
no treatm	4	0.82
Total	8	8.00

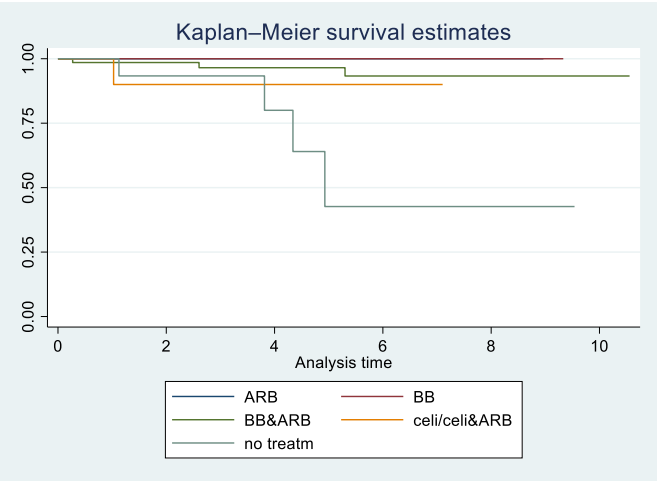
chi2(5) = 52.42
Pr>chi2 = 0.0000

aplan-Meier survivor function
y variable: endtreat

Time	Beg. total	Fail	Survivor function	Std. error	[95% conf.	int.]
ARB						
1	17	0	1.0000	.	.	.
2	12	0	1.0000	.	.	.
3	8	0	1.0000	.	.	.
4	6	0	1.0000	.	.	.
5	5	0	1.0000	.	.	.
6	3	0	1.0000	.	.	.
7	2	0	1.0000	.	.	.
8	2	0	1.0000	.	.	.
9	1	0	.	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
BB						
1	0	0	1.0000	.	.	.
2	6	0	1.0000	.	.	.
3	5	0	1.0000	.	.	.
4	5	0	1.0000	.	.	.
5	5	0	1.0000	.	.	.
6	3	0	1.0000	.	.	.
7	3	0	1.0000	.	.	.
8	2	0	1.0000	.	.	.
9	2	0	1.0000	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
BB&ARB						
1	67	1	0.9853	0.0146	0.9002	0.9979
2	57	0	0.9853	0.0146	0.9002	0.9979
3	48	1	0.9652	0.0245	0.8656	0.9913
4	39	0	0.9652	0.0245	0.8656	0.9913
5	34	0	0.9652	0.0245	0.8656	0.9913
6	27	1	0.9330	0.0395	0.7949	0.9793
7	18	0	0.9330	0.0395	0.7949	0.9793
8	6	0	0.9330	0.0395	0.7949	0.9793
9	4	0	0.9330	0.0395	0.7949	0.9793
10	2	0	0.9330	0.0395	0.7949	0.9793
11	1	0	.	.	.	.
celi						
1	0	0	1.0000	.	.	.
2	1	1	.	.	.	.
3	1	0	.	.	.	.
4	1	0	.	.	.	.
5	1	0	.	.	.	.
6	1	0	.	.	.	.
7	1	0	.	.	.	.
8	1	0	.	.	.	.
9	1	0	.	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
celi&ARB						
1	0	0	1.0000	.	.	.
2	8	0	1.0000	.	.	.
3	4	0	1.0000	.	.	.
4	3	0	1.0000	.	.	.
5	2	0	1.0000	.	.	.
6	2	0	1.0000	.	.	.
7	2	0	1.0000	.	.	.
8	1	0	.	.	.	.
9	1	0	.	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
no treatm						
1	0	0	1.0000	.	.	.
2	14	1	0.9333	0.0644	0.6126	0.9903
3	10	0	0.9333	0.0644	0.6126	0.9903
4	7	1	0.8000	0.1352	0.3735	0.9507
5	3	2	0.4267	0.2113	0.0698	0.7614
6	2	0	0.4267	0.2113	0.0698	0.7614
7	2	0	0.4267	0.2113	0.0698	0.7614
8	2	0	0.4267	0.2113	0.0698	0.7614
9	2	0	0.4267	0.2113	0.0698	0.7614
10	1	0	.	.	.	.
11	1	0	.	.	.	.

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

b) By treatment group with celiprolol and celiprolol&ARB groups merged



Equality of survivor functions
Log-rank test

fiveendtreat	Observed events	Expected events
ARB	0	0.86
BB	0	0.59
BB&ARB	3	5.31
celi/celi&ARB	1	0.42
no treatm	4	0.82
Total	8	8.00

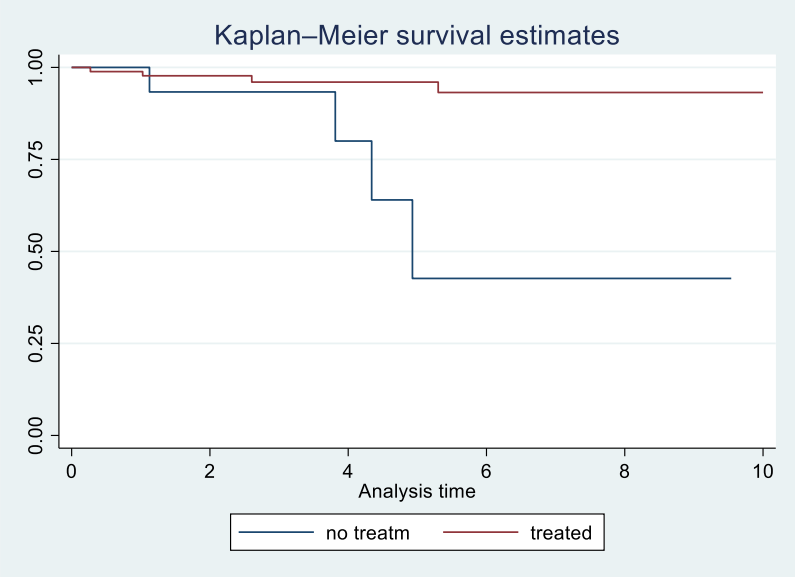
chi2(4) = 15.79
Pr>chi2 = 0.0033

Kaplan-Meier survivor function
By variable: fiveendtreat

Time	Beg. total	Fail	Survivor function	Std. error	[95% conf.	int.]
ARB						
1	17	0	1.0000	.	.	.
2	12	0	1.0000	.	.	.
3	8	0	1.0000	.	.	.
4	6	0	1.0000	.	.	.
5	5	0	1.0000	.	.	.
6	3	0	1.0000	.	.	.
7	2	0	1.0000	.	.	.
8	2	0	1.0000	.	.	.
9	1	0	.	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
BB						
1	0	0	1.0000	.	.	.
2	6	0	1.0000	.	.	.
3	5	0	1.0000	.	.	.
4	5	0	1.0000	.	.	.
5	5	0	1.0000	.	.	.
6	3	0	1.0000	.	.	.
7	3	0	1.0000	.	.	.
8	2	0	1.0000	.	.	.
9	2	0	1.0000	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
BB&ARB						
1	67	1	0.9853	0.0146	0.9002	0.9979
2	57	0	0.9853	0.0146	0.9002	0.9979
3	48	1	0.9652	0.0245	0.8656	0.9913
4	39	0	0.9652	0.0245	0.8656	0.9913
5	34	0	0.9652	0.0245	0.8656	0.9913
6	27	1	0.9330	0.0395	0.7949	0.9793
7	18	0	0.9330	0.0395	0.7949	0.9793
8	6	0	0.9330	0.0395	0.7949	0.9793
9	4	0	0.9330	0.0395	0.7949	0.9793
10	2	0	0.9330	0.0395	0.7949	0.9793
11	1	0	.	.	.	.
celi/celi&ARB						
1	0	0	1.0000	.	.	.
2	8	1	0.9000	0.0949	0.4730	0.9853
3	4	0	0.9000	0.0949	0.4730	0.9853
4	3	0	0.9000	0.0949	0.4730	0.9853
5	2	0	0.9000	0.0949	0.4730	0.9853
6	2	0	0.9000	0.0949	0.4730	0.9853
7	2	0	0.9000	0.0949	0.4730	0.9853
8	1	0	.	.	.	.
9	1	0	.	.	.	.
10	1	0	.	.	.	.
11	1	0	.	.	.	.
no treatm						
1	0	0	1.0000	.	.	.
2	14	1	0.9333	0.0644	0.6126	0.9903
3	10	0	0.9333	0.0644	0.6126	0.9903
4	7	1	0.8000	0.1352	0.3735	0.9507
5	3	2	0.4267	0.2113	0.0698	0.7614
6	2	0	0.4267	0.2113	0.0698	0.7614
7	2	0	0.4267	0.2113	0.0698	0.7614
8	2	0	0.4267	0.2113	0.0698	0.7614
9	2	0	0.4267	0.2113	0.0698	0.7614
10	1	0	.	.	.	.
11	1	0	.	.	.	.

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

c) Treated vs untreated excluding those with group III variant



Equality of survivor functions
Log-rank test

treatvsnot	Observed events	Expected events
no treatm	4	0.92
treated	4	7.08
Total	8	8.00

chi2(1) = 11.87
Pr>chi2 = 0.0006

Kaplan-Meier survivor function
By variable: treatvsnot

Time	Beg. total	Fail	Survivor function	Std. error	[95% conf.	int.]
no treatm						
1	0	0	1.0000	.	.	.
2	14	1	0.9333	0.0644	0.6126	0.9903
3	10	0	0.9333	0.0644	0.6126	0.9903
4	7	1	0.8000	0.1352	0.3735	0.9507
5	3	2	0.4267	0.2113	0.0698	0.7614
6	2	0	0.4267	0.2113	0.0698	0.7614
7	2	0	0.4267	0.2113	0.0698	0.7614
8	2	0	0.4267	0.2113	0.0698	0.7614
9	2	0	0.4267	0.2113	0.0698	0.7614
10	1	0	.	.	.	.
11	1	0	.	.	.	.
treated						
1	89	1	0.9886	0.0113	0.9221	0.9984
2	72	1	0.9773	0.0159	0.9122	0.9943
3	54	1	0.9601	0.0231	0.8785	0.9873
4	45	0	0.9601	0.0231	0.8785	0.9873
5	40	0	0.9601	0.0231	0.8785	0.9873
6	29	1	0.9319	0.0357	0.8150	0.9760
7	19	0	0.9319	0.0357	0.8150	0.9760
8	6	0	0.9319	0.0357	0.8150	0.9760
9	4	0	0.9319	0.0357	0.8150	0.9760
10	1	0	0.9319	0.0357	0.8150	0.9760
11	1	0	.	.	.	.

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.