



HAL
open science

Gastrointestinal bleeding from angiodysplasia in von Willebrand disease: Improved diagnosis and outcome prediction using videocapsule on top of conventional endoscopy

Antoine Rauch, Camille Paris, Yohann Repesse, Julien Branche, Roseline D'oiron, Annie Harroche, Catherine Ternisien, Sabine-marie Castet, Aurélien Lebreton, Brigitte Pan-Petes, et al.

► **To cite this version:**

Antoine Rauch, Camille Paris, Yohann Repesse, Julien Branche, Roseline D'oiron, et al.. Gastrointestinal bleeding from angiodysplasia in von Willebrand disease: Improved diagnosis and outcome prediction using videocapsule on top of conventional endoscopy. *Journal of Thrombosis and Haemostasis*, 2021, 19 (2), pp.380-386. 10.1111/jth.15155 . hal-04357418

HAL Id: hal-04357418

<https://hal.science/hal-04357418>

Submitted on 3 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Article type: Brief report

Gastrointestinal bleeding from angiodysplasia in von Willebrand disease: improved diagnosis and outcome prediction using videocapsule on top of conventional endoscopy

A. Rauch^{*†}, C. Paris^{*}, Y. Repesse[‡], J.Branche[§], R. D'Oiron[¶], A. Harroche^{**}, C. Ternisien^{††}, S. Castet^{‡‡}, A. Lebreton^{§§}, B. Pan-Petes^{¶¶}, F. Volot^{***}, S. Claeysens^{†††}, P. Chamouni^{‡‡‡}, V. Gay^{§§§}, C. Berger^{¶¶¶}, D. Desprez^{****}, C. Falaise^{††††}, C. Biron Andreani^{‡‡‡‡}, C Marichez^{*}, B. Pradines^{*†}, C.Zawadzki^{*}, N. Itzhar Baikian^{§§§§}, A. Borel-Derlon[‡], J. Goudemand^{*}, R.Gerard[§], S. Susen^{*†}
for the French Reference Center on von Willebrand Disease.

CHU Lille, Hematology Transfusion, LILLE, France, †INSERM, U1011, Univ. Lille, U1011-EGID, Institut Pasteur de Lille, LILLE, France, ‡Laboratoire d'hématologie, CHU de Caen, Caen, France, §CHU Lille, Gastroenterology Department, LILLE, France, ¶Center for Hemophilia and Rare Congenital Bleeding Disorders, University Hospital Paris-Sud, AP-HP, Bicêtre Hospital, Le Kremlin-Bicêtre, France, **Hôpital Necker Enfants Malades APHP, Paris, France, ††CHU Nantes, Laboratoire d'Hématologie, Nantes, France, ‡‡CHU Bordeaux Pellegrin, Bordeaux, France, §§CHU Clermont Ferrand, Clermont Ferrand, France, ¶¶Unité Hémostase clinique, Service Hématologie CHU Brest, Brest, France, *CHU Dijon, Dijon, France, †††CHU Toulouse, Toulouse, France, ‡‡‡CHU Rouen, Rouen, France, §§§CH Métropole Savoie - Site de Chambéry, Chambéry, France, ¶¶¶CHU Saint-Etienne, St Etienne, France, ****CHU Strasbourg, Strasbourg, France, ††††Hôpital de La Timone, AP-HM, Centre régional de traitement des hémophiles, Marseille, France, ‡‡‡‡Laboratoire d'Hématologie, CHU Montpellier, Montpellier, France, §§§§GH St-Louis Lariboisière F.Widal - Hôpital Lariboisière APHP, Laboratoire d'Hématologie, Paris, France.*

Corresponding author:

Sophie Susen, MD., Ph.D.

CHU Lille, Hematology Transfusion, Lille, France

INSERM, U1011, Univ. Lille, U1011 EGID, Institut Pasteur de Lille, Lille, France

Coordinator of the French Reference Center on von Willebrand Disease

Email: sophiesusen@aol.com

Short title: Video capsule endoscopy to predict outcome in VWD-patients with GI-bleeding

Keywords: angiodysplasia, argon plasma coagulation, gastrointestinal bleeding, video capsule endoscopy, von Willebrand disease

Abbreviations:

APC= Argon plasma coagulation, VWD= Von Willebrand disease, VWF= von Willebrand factor, GI= gastrointestinal, HMW= high-molecular-weight, MHEMO= French-network on inherited bleeding disorders, VCE= video capsule endoscopy

Essentials :

- In VWD no specific guidelines are dedicated to endoscopic exploration of GI-bleeding
- VCE on top of conventional endoscopy improves the diagnostic yield for angiodysplasia in VWD
- Patients with small-bowel angiodysplasia have a higher risk of re-bleeding at one year
- Patients with obscure or recurrent GI-bleeding should benefit from a more systematic use of VCE

Summary

Background: Despite a high prevalence of angiodysplasia, no specific guidelines are available for the modalities of endoscopic exploration of GI-bleeding in VWD. Whether VWD-patients could benefit from video capsule endoscopy (VCE) looking for angiodysplasia eligible to endoscopic treatment or at high risk of bleeding is unknown.

Objectives: To assess the diagnostic efficacy for angiodysplasia and the prognostic value of VCE on top of conventional endoscopy in VWD-patients with GI-bleeding.

Patients/Methods: A survey was sent to the 30 centers of the French-network on inherited bleeding disorders (MHEMO) to identify VWD-patients referred for endoscopic exploration of GI-bleeding from January-2015 to December-2017. Data obtained included patient characteristics, VWD phenotype/genotype, GI-bleeding pattern, results of endoscopic investigations and medical management applied including endoscopic therapy. We assessed by Kaplan-Meier analysis the recurrence-free survival after the first GI-bleeding event according to endoscopic categorization and, in patients with angiodysplasia, to the presence of small-bowel localizations on VCE-exploration.

Results: GI-bleeding source localization was significantly improved when including VCE-exploration ($p < 0.01$), even in patients without history of angiodysplasia ($p < 0.05$). Patients with angiodysplasia had more GI-bleeding recurrences ($p < 0.01$). A lower recurrence-free survival was observed in patients with angiodysplasia (log rank test, $p = 0.02$), and especially when lesions were located in the small-bowel (log rank

test, $p < 0.01$), even after endoscopic treatment with argon plasma coagulation (log rank test, $p < 0.01$).

Conclusion: VCE should be more systematically used in VWD-patients with unexplained or recurrent GI-bleeding looking for angiodysplasia eligible to endoscopic treatment or at high risk of relapse.

Introduction

Gastrointestinal (GI-) bleeding is the most frequent cause of hospitalization in von Willebrand Disease (VWD) [1, 2]. VWD-patients often present with recurrent overt or occult GI-bleeding from an unidentified source on conventional endoscopy [3]. This clinical picture is assumed to be related to an increased incidence of GI-angiodyplasia in VWD [4]. The mechanism could involve a dysregulated angiogenesis related to the lack of von Willebrand factor (VWF) high-molecular-weight (HMW) multimers [5-7] as GI-bleeding from angiodyplasia is more frequent in VWD type 2A, 2B and 3 [8, 9] and in acquired von Willebrand syndrome [10,11]. The management of angiodyplasia has been revolutionized with the advent of video capsule endoscopy (VCE) which is now the gold standard investigation to detect small-bowel angiodyplasia when no GI-bleeding source is identified after conventional endoscopy and to screen for lesions eligible to argon plasma coagulation (APC), the most effective endoscopic therapy [12,13]. Despite a high prevalence of angiodyplasia in VWD, no specific guidelines are available for the modalities of GI-tract exploration in patients with GI-bleeding. Current endoscopic exploration in these patients relies on a non-standardized strategy and its efficiency to predict outcome remains poorly reported.

Aims:

To investigate in current practice the diagnostic efficacy for angiodyplasia detection and the prognostic value of implementing VCE on top of conventional endoscopy in VWD-patients with GI-bleeding.

Methods:

A survey was sent to the 30 centers involved in the French-network on inherited bleeding disorders (MHEMO) to identify VWD-patients referred for endoscopic exploration of at least one GI-bleeding from January-2015 to December-2017 and describe the practices. Follow-up period was limited to 3-years because of rapid changes in devices allowing endoscopic treatment [14]. Only VWD-patients fulfilling the inclusion criteria of the French reference center for VWD [15] were included. VWD diagnosis was confirmed centrally in all patients including genotyping. GI-bleeding episode was defined as any overt or occult GI-bleeding (unexplained iron deficiency anemia causing a drop of hemoglobin level by more than 2g/dL from baseline). We analyzed patient characteristics, VWD type/subtype, GI-bleeding pattern, nature (gastroscopy, colonoscopy or VCE) and results of the endoscopic exploration and management that was applied: endoscopic therapy by APC, on-demand/prophylactic-VWF replacement therapy, use of antiangiogenic drugs. If angiodysplasia without another bleeding source was identified, GI-bleeding was categorized as “angiodysplasia”. GI-bleeding was categorized as “no-angiodysplasia” if another lesion was identified and as “obscure GI-bleeding” if no bleeding source was identified. Patients with angiodysplasia were categorized as “new additional angiodysplasia” or “*de novo* angiodysplasia” whether there was or not pre-existing angiodysplasia at start of follow-up. Recurrence was defined as evidence of overt or occult GI-bleeding (drop of hemoglobin level by more than 2g/dL from baseline). The study was approved by the institutional data protection authority of all participating centers (CNIL registration number DEC19-252).

Continuous variables were expressed as mean (\pm SEM or SD) or median (with interquartile range, [IQR]) and categorical data as n (%). Univariate analysis involved Mann-Whitney test for continuous variables and Chi-square or Fisher tests for binary variables. We assessed by Kaplan-Meier analysis the recurrence-free survival after the first GI-bleeding event according to endoscopic categorization and in patients with angiodysplasia the rate of GI-bleeding recurrence according to the presence of small-bowel localizations on VCE-exploration. Statistical analysis was performed with SPSS® software. Differences with p-value<0.05 were considered significant.

Results and discussion

Seventy seven percent of the MHEMO-centers answered the survey allowing further analysis of each individual case. All centers had access to the full set of endoscopic exploration including VCE. Patient characteristics and results are summarized in Table 1. A total of 127 GI-bleeding episodes were reported in 50 patients (mean=0.84 GI-bleeding episode per patient-year). At inclusion, 20% had pre-existing angiodysplasia, 16% were receiving VWF prophylaxis (with GI-bleeding as primary indication in half of them), 8% were treated with antiangiogenic drugs (octreotide, n=2; atorvastatine, n=2) and 8% with anti-thrombotic drugs.

During follow-up, angiodysplasia were identified endoscopically in 46% of patients confirming angiodysplasia as the leading cause of GI-bleeding in VWD [2]. Patients with angiodysplasia were older than patients with obscure GI-bleeding (p=0.002) and their most frequent presentation was melena. A total of 5 children, VWD type 2A (n=2) or type 3 (n=3), were explored for GI-bleeding. The bleeding source wasn't identified in 3 children while a diagnosis of gastric angiodysplasia and anal fissure was established in the others. GI-bleeding and angiodysplasia were more frequently

observed in VWD-patients with type 2A, 2B or 3 compared to patients without HMW-multimers defect (respectively n=40/815 versus n=10/1082, $p<0.0001$; and n=17/815 versus 6/108, $p=0.005$).

GI-bleeding management in VWD-patients with angiodysplasia is challenging due to the severity and the recurrence of bleeding episodes [16, 17]. Off-label use of antiangiogenic drugs is sometimes considered in patients with refractory GI-bleeding [18, 19]. In our cohort, 73% of patients with angiodysplasia or obscure GI-bleeding were treated prophylactically with either VWF-containing concentrates (n=15), antiangiogenic drugs (octreotide, n=4; atorvastatine, n=3) or both (VWF prophylaxis and octreotide, n=3) during follow-up. VWF prophylaxis was more frequently introduced or intensified for GI-bleeding in patients with angiodysplasia or obscure GI-bleeding compared to patients with no-angiodysplasia (43%, 72% and 6%; $p=0.01$ and $p<0.001$ respectively).

The sequential endoscopic investigations during follow-up are summarized in Figure 1. All patients were explored at least once with conventional endoscopy. Overall, angiodysplasia were identified in 26% of patients after conventional endoscopy: new additional angiodysplasia were identified in 50% of patients with pre-existing angiodysplasia and *de novo* angiodysplasia in 20% of patients without pre-existing angiodysplasia, a proportion in line with a recent study also reporting the frequency of angiodysplasia on conventional endoscopy [2]. Besides angiodysplasia, other lesions were identified in 32% of patients after conventional endoscopy (for details see Table 1). In the remaining 42% of patients, the bleeding source wasn't identified after conventional endoscopy. This high proportion of VWD-patients still having a negative exploration after conventional endoscopy highlights the need for a more systematic and multimodal approach to identify angiodysplasia [12, 13]. Among these

21 patients without bleeding source identification after conventional endoscopy, 15 underwent at least one VCE-exploration and angiodysplasia were identified in 10/15 (66%) of them. In patients with angiodysplasia lesions already identified after conventional endoscopy, synchronous small-bowel lesions were identified in 3/8 (38%) of patients who underwent at least one VCE-exploration. No difference in VCE-referral was observed whether patients had pre-existing bleeding angiodysplasia or not (6/10 and 19/40 patients respectively, $p=0.48$). A trend for more GI-bleeding events was observed in patients referred for VCE compared to patients without VCE-referral (3 ± 2.1 , $n=25$ versus 2 ± 1.5 , $n=11$; $p=0.11$).

No adverse events associated with VCE-exploration were reported. Although all the patients eligible to VCE-exploration were not investigated, *de novo* angiodysplasia were identified in 40% of patients without pre-existing angiodysplasia and new additional angiodysplasia in 70% of patients with pre-existing angiodysplasia when combining VCE to conventional endoscopy (Table 1). Overall, the endoscopic localization of the bleeding source was significantly improved when using VCE-exploration ($p<0.01$). This result remained significant even after excluding the 10 patients with pre-existing angiodysplasia ($p<0.05$). In our cohort, VCE allowed to further identify angiodysplasia in two third of patients with negative conventional endoscopy. It should be noted that of the 11 patients with obscure GI-bleeding at the end of the follow-up who should have been further explored, 6 were not investigated despite VCE availability. This suggests a need for dedicated guidelines for endoscopic exploration in VWD-patients with GI-bleeding strengthening the role for VCE on top of conventional endoscopy.

No death related to GI-bleeding occurred during follow-up. A high rate of recurrence was observed (median per patient= $1[0-2]$, range: 0-7). At least one recurrence was

observed in 58% of patients and 32% of them had at least 2 recurrences. The frequency of recurrences was higher in patients with angiodysplasia compared to patients with another bleeding lesion (log rank test, $p=0.02$; Fig 2A).

At least one complete revision of the GI-tract, including VCE-exploration, was performed in 18 patients with angiodysplasia during their follow-up. More GI-bleeding recurrences were observed in patients with small-bowel angiodysplasia on VCE than in patients with without such localization (median=2.5 [2-4.5], $n=12$ versus 0[0-1], $n=6$; $p<0.01$) while there was no significant difference in age and duration of follow-up between both groups. Accordingly, a lower survival rate before first GI-bleeding recurrence was observed in patients with small-bowel angiodysplasia (log-rank test, $p<0.01$), with most of them having their first recurrence within 12 months (Fig 2B).

Eighteen patients with angiodysplasia (78%) were treated at least once with APC for a total of 22 procedures. GI-bleeding relapsed in 55% of these patients and following 50% of procedures. VCE status was available for 13 patients treated with APC (through conventional endoscopy [$n=11$] or double-balloon enteroscopy [$n=2$]). The median time to re-bleeding after APC of gastric, duodenal or colonic angiodysplasia was 6.5 months in patients having a concomitant small-bowel lesion ineligible to APC ($n=7$) whereas only one of the six patients without such localization relapsed after 21 months (log rank test, $p<0.01$). Three patients with angiodysplasia relapsed while on antithrombotics suggesting that recurrence may also be medication related.

In our cohort, there was a large heterogeneity in the duration and intensity of the VWF prophylaxis regimen. However, an increased use of VWF prophylaxis and/or antiangiogenic drugs was observed during follow-up in patients with small-bowel angiodysplasia compared to other angiodysplasia patients without such localization (10/12, 83% and 2/6, 33% respectively; $p=0.03$). Antiangiogenic treatment was

initiated in 6 patients with 5 of them having small-bowel angiodysplasia ineligible to APC. These data suggest that the presence of small-bowel lesions inaccessible to endoscopic treatment is associated with a worse outcome [4, 20] and should be included in the decision to introduce or intensify VWF prophylaxis or to use antiangiogenics. Identifying a lesion on endoscopy doesn't prove this lesion is the cause of GI-bleeding unless active or signs of recent bleeding are also identified. The detection of nonbleeding angiodysplasia is likely to be higher when repeating endoscopic investigations including VCE. In non-VWD patients, the prevalence of incidental colonic angiodysplasia is rare, and these lesions are characterized by a benign course with almost no recurrence at 3 years [21]. By contrast in our cohort, patients with angiodysplasia had more GI-bleeding recurrence and an increased need for VWF replacement therapy or antiangiogenic drugs. Moreover, the endoscopic treatment of lesions accessible to APC was efficient in half of the patients to prevent further GI-bleeding. These data provide indirect evidence of the clinical relevance of these lesions in VWD-patients.

Altogether our results provide evidence that using VCE on top of conventional endoscopy in VWD-patients with GI-bleeding improves the diagnostic yield for angiodysplasia and outcome prediction. Our results support a more intensive exploration of the GI-tract in VWD-patients with unexplained or recurrent GI-bleeding with a systematic use of VCE allowing to identify new lesions eligible for local endoscopic treatment or helping to adapt medical treatment.

As relapse may not only indicate failure of endoscopic treatment but also the presence of untreated lesions, such endoscopic strategy aiming to optimize the identification and treatment of angiodysplasia could limit the GI-bleeding recurrences and improve outcomes in VWD-patients.

Two large academic centers (representing 21% of the cohort) accounted for 12 of the 25 patients referred for VCE. It could be related to an increased awareness of angiodysplasia burden in VWD leading to a closer collaboration between hematologists and gastroenterologists in largest centers. This inter-center heterogeneity reflects real-life data and underlines the need for specific guidelines dedicated to the modalities of endoscopic exploration in VWD-patients with GI-bleeding.

Conclusion

VWD-patients with GI-bleeding could benefit from a better standardized management with a more systematic use of VCE looking for angiodysplasia eligible to endoscopic treatment or at high risk of relapse. VCE could be useful to improve the diagnostic yield of angiodysplasia and to tailor the intensity and duration of VWF prophylaxis and the schedule of the endoscopic follow-up considering also VWD severity. Whether such a management taking into account the multifocal localization of gastrointestinal angiodysplasia could translate into improved outcomes in VWD deserves further studies. A multidisciplinary approach including close collaboration between hematologists and gastroenterologists and access to full set of endoscopic procedures should be the standard of care in VWD-patients with GI-bleeding.

Conflict of interest: The authors declared no conflict of interest.

Author contributions: A.Rauch designed the study, conducted the data analysis and wrote the manuscript. C. Paris, Y. Repesse, J.Branche, R. D'Oiron, A. Harroche, C. Ternisien, S. Castet, A. Lebreton, B. Pan-Petes, F. Volot, S. Claeysens, P. Chamouni, V. Gay, C. Berger, D. Desprez, C. Falaise, C. Biron Andreani, C Marichez, B. Pradines, C.Zawadzki, N. Itzhar Baikian, A. Borel-Derlon, J. Goudemand and R.Gerard conducted the data collection and critically reviewed the

manuscript. S. Susen designed the study, conducted data analysis and critically reviewed the manuscript.

References

- 1) Holm E, Carlsson KS, Lövdahl S, Lail AE, Abshire TC, Berntorp E. Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: Results from national registers in Sweden compared with normal controls and participants in the von Willebrand Disease Prophylaxis Network. *Haemophilia*. 2018; 24:628-633.
- 2) Tsagianni A, Comer DM, Yabes JG, Ragni MV. Von Willebrand disease and gastrointestinal bleeding: A national inpatient sample study. *Thromb Res*. 2019; 178:119-123.
- 3) Franchini M, Mannucci PM. Von Willebrand disease-associated angiodysplasia: a few answers, still many questions. *Br J Haematol*. 2013; 161:177-82.
- 4) Jackson CS, Gerson LB. Management of gastrointestinal angiodysplastic lesions (GIADs): a systematic review and meta-analysis. *Am J Gastroenterol*. 2014; 109:474-83.
- 5) Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, et al. Endothelial von Willebrand factor regulates angiogenesis. *Blood*. 2011; 117:1071-80.
- 6) Starke RD, Paschalaki KE, Dyer CE, Harrison-Lavoie KJ, Cutler JA, McKinnon TA, et al. Cellular and molecular basis of von Willebrand disease: studies on blood outgrowth endothelial cells. *Blood*. 2013; 121:2773-84.
- 7) Randi AM, Smith KE, Castaman G. von Willebrand factor regulation of blood vessel formation. *Blood*. 2018; 132:132-140.
- 8) Fressinaud E, Meyer D. International survey of patients with von Willebrand disease and angiodysplasia. *Thromb Haemost*. 1993; 70:546.
- 9) Castaman G, Federici AB, Tosetto A, La Marca S, Stufano F, Mannucci PM, Rodeghiero F. Different bleeding risk in type 2A and 2M von Willebrand disease: a 2-year prospective study in 107 patients. *J Thromb Haemost*. 2012; 10:632-8.
- 10) Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*. 2003; 349:343-9.
- 11) Blackshear JL, Stark ME, Agnew RC, Moussa ID, Safford RE, Shapiro BP, et al. Remission of recurrent gastrointestinal bleeding after septal reduction therapy in patients with hypertrophic obstructive cardiomyopathy-associated acquired von Willebrand syndrome. *J Thromb Haemost*. 2015; 13:191-6.
- 12) Raju GS, Gerson L, Das A, Lewis B. American Gastroenterological Association. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. *Gastroenterology*. 2007; 133:1694-6.
- 13) Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding. *Am J Gastroenterol*. 2015; 110:1265-87.
- 14) Dioscoridi L, Forti E, Pugliese F, Cintolo M, Italia A, Mutignani M. Thulium laser coagulation: a new effective endotherapy to treat gastrointestinal angiodysplasia. *Gastrointest Endosc*. 2019; 90:319-320.
- 15) Veyradier A, Boisseau P, Fressinaud E, Caron C, Ternisien C, Giraud M, Zawadzki C, Trossaert M, Itzhar-Baikian N, Dreyfus M, d'Oiron R, Borel-Derlon A, Susen S, Bezieau S, Denis CV, Goudemand J; French Reference Center for von Willebrand disease. A Laboratory Phenotype/Genotype Correlation of 1167 French Patients From 670 Families With von Willebrand Disease: A New Epidemiologic Picture. *Medicine (Baltimore)*. 2016; 95:e3038.

- 16) Makris M, Federici AB, Mannucci PM, Bolton-Maggs PH, Yee TT, Abshire T, Berntorp E. The natural history of occult or angiodysplastic gastrointestinal bleeding in von Willebrand disease. *Haemophilia*. 2015; 21:338-42.
- 17) Abshire T, Cox-Gill J, Kempton CL, Leebeek FW, Carcao M, Kouides P, et al. Prophylaxis escalation in severe von Willebrand disease: a prospective study from the von Willebrand Disease Prophylaxis Network. *J Thromb Haemost*. 2015; 13:1585-9.
- 18) Sohal M, Laffan M. Von Willebrand disease and angiodysplasia responding to atorvastatin. *Br J Haematol*. 2008; 142:308-9.
- 19) Bowers M, McNulty O, Mayne E. Octreotide in the treatment of gastrointestinal bleeding caused by angiodysplasia in two patients with von Willebrand's disease. *Br J Haematol*. 2000; 108:524-7.
- 20) Sakai E, Endo H, Taguri M, Kawamura H, Taniguchi L, Hata Y, et al. Frequency and risk factors for rebleeding events in patients with small bowel angioectasia. *BMC Gastroenterol*. 2014; 14:200.
- 21) Foutch PG, Rex DK, Lieberman DA. Prevalence and natural history of colonic angiodysplasia among healthy asymptomatic people. *Am J Gastroenterol*. 1995; 90:564-7.

Legend of table and figures

Fig 1: Diagnosis yield of video capsule on top of conventional endoscopy in VWD-patients with GI-bleeding

A) Flow diagram of sequential endoscopic explorations detailing for both patients with and without pre-existing angiodysplasia at the start of follow-up the proportion of patients who completed VCE and the results of endoscopic exploration (angiodysplasia, other bleeding lesion or obscure GI-bleeding). Six patients categorized as obscure GI-bleeding were not investigated by VCE despite negative finding on CE.

B) Diagnostic yield of CE+VCE endoscopic strategy compared to CE alone for angiodysplasia: in all VWD-patients (n=50, Chi-square test, **p<0.01) and in VWD-patients without pre-existing angiodysplasia at start of follow-up (n=40, Chi-square test, *p<0.05).

CE: conventional endoscopy, GI: gastrointestinal, OGIB: obscure GI-bleeding; VCE: video capsule endoscopy

Fig 2: Risk stratification of GI-bleeding recurrence in VWD-patients with GI-bleeding

A) Comparison of the recurrence-free survival after the first GI-bleeding event according to final endoscopic categorization as “angiodysplasia”, “obscure GI-bleeding” or “no angiodysplasia”. The recurrence rate was significantly higher in patients with angiodysplasia compared to patients with another bleeding lesion (p=0.02, log rank test).

B) Comparison of the recurrence-free survival after the first GI-bleeding event in patients with (n=12: VWD type 1 [n=1], 2A [n=5], 2B [n=3], 2M [n=1], 2N [n=1] and 3 [n=1]) or without small-bowel angiodysplasia (n=6: VWD type 2A [n=2], 2B [n=1] and 2M [n=3]) on VCE[†]. The recurrence rate was significantly higher in the presence of small-bowel angiodysplasia (p=0.005, log rank test).

[†]*Analysis restricted to the 18 angiodysplasia patients who underwent at least one complete revision of their gastrointestinal tract (including VCE-exploration) during their follow-up. Of the 13 patients with a positive VCE, 12 had a small-bowel localization and one patient a gastric lesion.*

Table 1: Clinical characteristics according to endoscopic categorization

Variables	All (n=50)	Angiodysplasia (n=23)	No-angiodyplasia (n=16)	Obscure GI-bleeding (n=11)	p-value
Age (median, IQR)	61 [40-68]	65 [49-70]	47 [38-69]	46 [13-62]	0.06*, 0.002 [†]
Male/female	26/24	13/10	8/8	5/6	ns [†]
VWD, n (relative % ^{‡‡})					
Type 1 ¹	1 (0.2%)	1 (0.2%)	0	0	
Type 2 ²					
2A	13 (3.5%)	9 (2.4%)	2	2	
2B	16 (4.2%)	5 (1.3%)	7	4	-
2M	8 (1.8%)	4 (0.9%)	3	1	
2N	1 (0.7%)	1 (0.7%)	0	0	
Type 3 ³	11 (16%)	3 (4.5%)	4	4	
VWF:Ag IU.dL ⁻¹ (median, IQR)	25 [10-40]	29 [15-50]	22 [3-35]	16 [0-40]	ns [†]
VWF:RCo IU.dL ⁻¹ (median, IQR)	10 [5-16]	8 [5-14]	12 [1-20]	10 [0-20]	ns [†]
FVIII:C IU.dL ⁻¹ (median, IQR)	32 [20-49]	33 [24-58]	34 [13-50]	31 [2-53]	ns [†]
Use of antithrombotic drugs, n	4	3 ^{**}	1 ^{††}	0	ns [†]
GI-bleeding					
GI-bleeding events, n (median, IQR) per patient	2 [1-3]	3 [1-4]	1 [1-2]	2 [1-2]	0.01*, 0.04 [†]
Patients with ≥ 1 GI-bleeding recurrence, n (%)	29 (58%)	17 (74%) ^{¶¶}	5 (31%)	7 (63%)	<0.001*, 0.04 [†]
Endoscopic procedures					
Gastroscopy, n (median, IQR) per patient	1 [1-2]	2 [1-3]	0.5 [0-1]	1 [1-2]	<0.001*, ns [†]
Coloscopy, n (median, IQR) per patient	1 [1-2]	1 [1-2]	1 [0.25-1]	1 [1-2]	ns [†]
Completion of VCE during follow-up, n (%)	25 (50%)	18 (78%)	2 (12.5%)	5 (45%)	
Lesions identified after conventional endoscopy					
Angiodysplasia	13/50				
New additional lesions [‡]	5/10	-	-	-	-
<i>De novo</i> angiodysplasia [§]	8/40				
Other lesions [¶]	16/50				
No diagnosis	21/50				
Lesions identified in patients negative after conventional endoscopy					

Angiodysplasia		10/15			
New additional lesions [‡]	-	2/3	-	-	-
<i>De novo</i> angiodysplasia [§]		8/12			
Medical management					
VWF prophylaxis					
At baseline, n (%)	8 (16%)	4 (17%)	1 (6%)	3 (27%)	
Introduction or intensification during follow-up, n (%)	19 (38%)	10 (43%)	1 (6%)	8 (72%)	
Antiangiogenic drugs					
At baseline, n (%)	4 (8%)	3 (13%)	0	1	
At the end of follow-up, n (%)	9 (18%)	8 (34%) ^{§§hh}	0	1	
Argon plasma coagulation, n (%)	-	18 (78%)	-	-	

*p-value for “no angiodysplasia” vs “angiodysplasia”, †p-value for “obscure GI-bleeding” vs “angiodysplasia”, ‡patients diagnosed with angiodysplasia with pre-existing angiodysplasia at start of follow-up, §patients diagnosed with angiodysplasia without pre-existing angiodysplasia at start of follow-up, ¶other lesions (n=1 unless otherwise stated) : peptic ulcer (n=5), hemorrhoidal bleeding (n=5), colorectal adenoma (n=3), colorectal adenocarcinoma, diverticular bleeding, anal fissure, **Aspirin for coronaropathy in a 67-year old male with VWD type 2A diagnosed with small-bowel angiodysplasia: no aspirin withdrawal, 3 relapses; Dual aspirin + clopidogrel therapy in a 68-year old female with VWD type 2M diagnosed with small-bowel angiodysplasia: 1 relapse after clopidogrel withdrawal; Apixaban uptake for atrial flutter in a 80-year old female with VWD 2N diagnosed with small-bowel angiodysplasia: after 2 recurrences under apixaban, a radiofrequency catheter ablation was performed in order to remove apixaban. No further relapse occurred after apixaban withdrawal; ††Fluindione uptake for atrial fibrillation in a 80-year old male with VWD type 2M diagnosed with gastric ulcer and diverticular polyposis: no fluindione withdrawal, 4 relapses; ††relative percentage of VWD-patients with GI-bleeding or angiodysplasia relative to the total number of VWD-patients followed in the centers who completed the survey; §§one patient stopped atorvastatine uptake before the end of follow-up owing to a lack of efficacy and the presence of muscular side-effects. ¶¶11/17 patients without pre-existing angiodysplasia and 6/7 patients with pre-existing angiodysplasia experienced repeated bleeding; ns: non-significant.

VWD genotyping (n=1 unless otherwise stated):

- Type 1¹: p.Arg1205Leu
- Type 2²: 2A: p.Tyr1146Cys, p.Glu1554_Gln1556del (n=2), p.Leu1580Pro, p.Leu1582Pro, p.Arg1583Trp/p.Tyr1584Cys, p.Arg1597Trp (n=3), p.Thr1608Pro, p.Val1665_Cys1669del, delExon17-19; 2B: p.Met1304dup (n=4), p.Arg1306Gln, p.Arg1306Trp, p.Arg1308Pro (n=2), p.Arg1308Cys, p.Val1316Met, p.Arg1341Gln (n=5), p.Ile1380Lys; Type 2M: p.Arg1315Cys (n=3), p.Arg1374Cys, p.Ser1378Phe, p.Tyr1735Asn, p.Leu1383Pro; Type 2N: p.Arg854Gln
- Type 3³: p.Arg273Trp/p.Gln1311*, p.Pro812Argfs*31homozygous, p.Arg34*/p.Arg960*, c.55+1G>T/p.Pro812Argfs*31, p.Pro1266Gln/p.Val1279Ile, p.Gln1311*/c.8254-10T>C, p.Gln1311* homozygous, delExon1-52 homozygous, p.Cys1130* homozygous, p.Glu2742*/c.8190_8253+1dup64, p.Arg447Trp/p.Cys2248Tyr/p.Leu2786Pro

