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Jan Michiels

Good Heart Centre, The Netherlands

Evaluation of classical and novel von Willebrand Factor assays in ECLM defined von Willebrand disease patients


A complete set of von Willebrand factor (VWF) assays is used for the diagnosis and classification of von Willebrand disease (VWD) according to European Clinical Laboratory and Molecular (ECLM) criteria (Clinical Applied Thrombosis/Hemostasis 2017;23(6):518). The aim is to evaluate the von Willebrand factor (VWF) assays VWF:GPIbM and VWF:GPIbR in von Willebrand disease (VWD) against the use of ECLM criteria as the gold standard for VWD classification anno 2018. Methods. The complete set of VWF assays include Platelet Function Analyser closure time (PFA-CT) von Willebrand factor (VWF) antigen (Ag), ristocetine cofactor activity (RCo), collagen binding (CB), propeptide (pp), ristocetine induced platelet aggregation (RIPA), the rapid VWF activity assay VWF:GPIbM based on glycoprotein Ib (GPIb) binding to particles coated with G233V and M239V mutants in the absence of ristocetin, the rapid VWF:GPIbR assay in the presence of ristocetine, and the responses to DDAVP of FVIII:C and VWF parameters to pick up secretion and/or clearance defects of VWF. It resulted in VWF:RCo/Ag, VWF:GPIbM/Ag and VWF:GPIbR ratios are completely normal (above 0.7) in all variants of VWD type 1 and Low VWF. The VWF:RCo/Ag, GPIbR/Ag and GPIbM/Ag ratios vary around the cut off level of 0.70 in VWD due to multimerization defect in the D3 domain and therefore diagnosed as either type 1 E or type 2E. The VWF:GPIbM/Ag and VWF:GPIbR/Ag ratios are pronounced decreased as compared to VWF:RCo/Ag and VWF:CB/Ag ratios in dominant VWD 2A and VWD 2B due to proteolytic loss of large and intermediate VWF multimers caused by VWF mutations in the A2 and A1 domain. VWD 2M due to loss of function mutation in the A3 domain is

featured by decreased VWF:RCo/Ag ratio and normal VWF:CB/Ag ratio, whereas the VWF:GPIbR/Ag ratio (range 0.14-28) and the VWF:GPIbM/Ag ratio (range 0.32 to 0.36) were decreased indicating the need to retain the VWF:CB assay to make a correct diagnosis of VWD 2M. The introduction of the rapid VWF:GPIbM or VWF:GPIbR assays as compared to the classical VWF:RCo assay did change VWD type 2 into type 1 in about 10 to 12%. VWD type 1 due to a heterozygous mutation in the D1 domain is featured by persistence of proVWF as the cause of VWF secretion/multimerization and FVIII binding defect mimicking VWD type 3 together with decreased values for VWFpp, VWFpp/Ag ratios. The majority of 22 different missense mutations in the D3 domain are of type 1 or 2 E multimerization defect usually associated with an additional secretion defect (increased FVIII:C/VWF:Ag ratio) and or clearance defect (increased VWFpp/Ag ratio). The majority of VWF mutations in the D4 and C1 to C6 are VWD type 1 SD with smeary (1sm) or normal (1m) multimers with no or a minor clearance defect. The heterozygous S2179F mutation in the D4 domain is featured by VWD type 1 secretion and clearance (SCD). Thus it is concluded that a complete set of sensitive FVIII:C and VWF assays related to domain location of the molecular defect is mandatory for correct diagnosis and classification of VWD.

Speaker Biography

Jan Michiels Professor of Nature Medicine & Health Blood Coagulation & Vascular Medicine Center in Netherlands. He also serves as an Editorial board member for many scientific journals.

e: goodheartcenter@upcmail.nl

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