# Inhibition of adamts13: a novel therapy to treat mechanical circulatory support-induced acquired von willebrand syndrome

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**Introduction:** Bleeding is the most frequent adverse event in patients with continuous flow mechanical circulatory support (CF-MCS) and has been linked to the occurrence of acquired von Willebrand syndrome (aVWS). MCS devices cause an increased shear-induced proteolysis of von Willebrand factor (VWF) by ADAMTS13, leading to aVWS. Hence, specifically blocking ADAMTS13 might be an efficient way to rescue the loss of HMW VWF multimers in CF-MCS patients.

**Purpose:** To investigate if blocking ADAMTS13, using an in-house developed inhibitory anti-ADAMTS13 monoclonal antibody (mAb), prevents the loss of high molecular weight (HMW) VWF multimers in in vitro CF-MCS systems and to determine the efficacy of this therapy in a CF-MCS calf model.

**Methods:** Human blood was perfused through in vitro CF-MCS systems (Heartmate II and Impella CP, axial flow heart pumps) in the presence of the inhibitory or control mAb (20 μg/mL). Bovine blood was perfused through an in vitro Impella 5.5 system with the inhibitory mAb (20 μg/mL) or PBS. Next, Impella 5.5 pumps were implanted in calves. One dose of the inhibitory mAb (600 μg/kg) or PBS was injected eight days after Impella implantation. Plasma samples were analysed for VWF multimers, VWF antigen (VWF:Ag) and VWF collagen binding activity (VWF:CB).

**Results:** A time-dependent decrease in HMW VWF multimers was observed in both in vitro CF-MCS systems in the presence of the control mAb, leading to a 70% reduction of HMW VWF multimers, 180 minutes (min) after blood perfusion (p=0.01 for HM II and p=0.0003 for Impella). This was also reflected by a severely decreased VWF:CB/VWF:Ag ratio (0.59±0.11 and 0.52±0.10 at 180 min versus 1.00±0.06 and 1.07±0.09 before perfusion, for the HM II (p=0.03) and Impella (p=0.001) respectively). Interestingly, blocking ADAMTS13 using the inhibitory mAb prevented the loss of HMW VWF multimers in both systems (p=0.50 for the HM II and p=0.06 for the Impella, 180 min after the start of perfusion). The preservation of HMW VWF multimers was also reflected by normal VWF:CB/VWF:Ag ratios (0.92±0.16 and 0.97±0.11 at 180 min versus 0.93±0.09 and 1.19±0.12 before perfusion for the HM II (p=0.75) and Impella (p=0.06) respectively). Blocking bovine ADAMTS13 using the inhibitory mAb could prevent the loss of HMW VWF multimers in the in vitro Impella 5.5 system, showing that the calf is a good preclinical animal model to study the in vivo effect of this novel therapy. Impella implantation in the calves led to a decrease in HMW VWF multimers (Figure 1A and B). Hence, this animal model represents the VWF laboratory features of MCS-induced aVWS. Moreover, the loss of HMW VWF multimers after pump implantation could be rescued after injection of the inhibitory mAb (Figure 1A and B).

**Conclusion:** Blocking ADAMTS13 rescues MCS-induced VWF proteolysis in calves. Hence, inhibiting ADAMTS13 function could become a promising therapeutic strategy to rescue aVWS-induced bleeding in MCS patients.

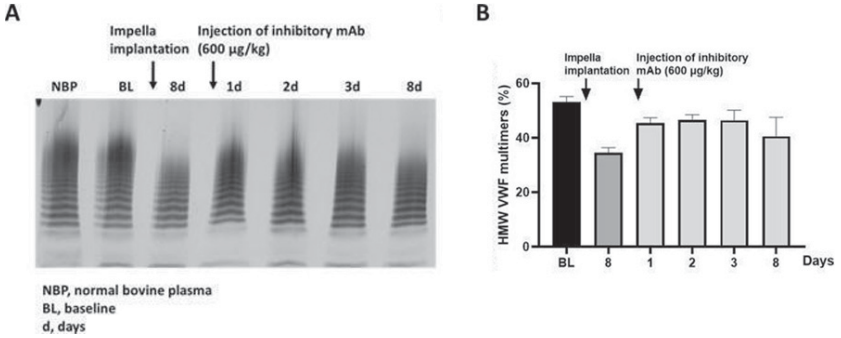


Figure 1. Impella calf model