Nanocomposites are the materials of the future with immense potential as biomedical devices. In a series of in vitro experiments, we assessed the anti-thrombogenic potential of polyhedral oligomeric silsesquioxane (POSS®)-nanocomposites at the vascular interface. Tests performed include thromboelastography, platelet adhesion assays, fibrinogen direct ELISA, anti-factor Xa assays as well as surface topographic analysis. Our results indicate that these nanocomposites exhibit lower levels of platelet and fibrinogen adsorption compared to conventional vascular prostheses such as PTFE. In addition, POSS®-nanocomposites possess an surface anti-factor Xa activity, similar to heparin, that is dependent on its concentrations. These unique characteristics may be attributed to their surface nanostructure and non-linearity. These findings may open entirely new vistas in biomedical engineering by sparking a materials revolution in vascular access devices.