Monoclonal antibodies (mAb) against PCSK9 lower plasma LDL-cholesterol levels by increasing the lifespan of LDL receptors (LDLR). Significant effects on lipoprotein(a) [Lp(a)] have also been observed, but the mechanism for this is neither known nor intuitive since Lp(a) is not cleared by LDLR. Our and other laboratories have shown that PCSK9 associates with LDL in plasma. Here, we aimed to study whether PCSK9 also associates with Lp(a) particles and whether this association depends on Lp(a) levels and/or apo(a) size. Using sandwich ELISA we determined that plasma PCSK9 is indeed associated with Lp(a) particles in patient with high Lp(a) levels (>30mg/dl). We then isolated LDL and Lp(a) fractions from plasma of 8 patients with high Lp(a) levels, ranging from 36 to 224 mg/dl, and determined PCSK9 and apoB levels as well as apo(a) isoforms. Our results show a 17.8 fold higher PCSK9/apoB ratio for Lp(a) compared with LDL (Fig. 1A), which suggests a preferential distribution of PCSK9 with Lp(a), at least in high Lp(a) individuals. Surprisingly, the preferential association of PCSK9 with Lp(a) was inversely correlated to Lp(a) levels (Fig. 1B) and independent of LDL levels. Since Lp(a) levels are inversely correlated with the size of apo(a), we set out to determine whether PCSK9 association with Lp(a) is related to the molecular weight of apo(a). Using plasma of patients with two distinct apo(a) isoforms, we show that PCSK9 associates exclusively with the higher molecular weight of apo(a) (Fig. 1C).

Our results suggest that Lp(a)-bound PCSK9 exists in plasma of patients with high Lp(a) and that this association depends on the size of apo(a). This provides a possible mechanism for the reduction in Lp(a) caused by PCSK9mAb, as immune complexes mAb-PCSK9-Lp(a) may be cleared via the mononuclear phagocyte system.