188

**DRUG-ELUTING STENTS CONTAINING IBUPROFEN:
A NOVEL STRATEGY TO REDUCE RESTENOSIS AND
PREVENT LATE IN-STENT THROMBOSIS**

A Giraldo, A Dannoura, I Pereira, P Dash, J Gibbins, G Brooks, K Bicknell *University of Reading*

doi:10.1136/heartjnl-2013-304019.188

Introduction Drug-eluting stents (DES) have reduced the rates of restenosis to less than 10%; however, increased incidence of late

in-stent thrombosis, is now a major clinical problem of using DES for its consequences in terms of morbidity and mortality. Interference with the process of re-endothelialization appears to play a major role in this latent complication. Thus, the search for molecular compounds capable of preventing restenosis that also can reduce the risk of late in-stent thrombosis is of utmost importance. Previously, we have shown that certain non-steroidal anti-inflammatory drugs (NSAIDs) are capable of inhibiting rat vascular smooth muscle cell proliferation, a key element in the process of restenosis post stent deployment. Here, we evaluated whether proliferation and migration of human coronary artery smooth muscle cells (HCASMCs) is reduced by the NSAID, ibuprofen, whether this correlated with changes in the phenotype of HCASMCs and the potential molecular mechanisms involved. Also, we investigated whether human coronary artery endothelial cell (HCAEC) migration was affected by ibuprofen.

Methods Cell proliferation was evaluated by trypan blue exclusion. Cell migration was assessed by wound healing assay and by time lapse videomicroscopy. Protein expression was assessed by immunoblotting and morphology by immunocytochemistry. The involvement of the PPAR γ pathway was studied with the selective agonist, troglitazone, and with the PPAR γ antagonists, PGF2 α and GW9662.

Results We show that ibuprofen inhibited proliferation as well as migration of HCASMCs in a dose-dependent manner (IC₅₀ of 680 and 410 μ M, respectively). Interestingly, we found that ibuprofen induced a switch in HCASMCs towards a differentiated phenotype, with a characteristic spindle shape, and a significant increase in the expression of contractile protein markers, e.g. SM α -actin, SM22 α and F-actin. PPAR γ antagonists, PGF2 α and GW9662, almost completely abrogated the proliferative and migratory responses of HCASMCs, as well the changes in morphology. However, PPAR γ antagonists did not affect the expression pattern of contractile proteins, suggesting that these effects are mediated by a PPAR γ -independent pathway. Importantly, ibuprofen did not affect migration of HCAECs even at high doses (up to 1000 μ M), suggesting that the effects of ibuprofen on HCASMCs are selective. Interestingly, the protein levels of PPAR γ are higher in HCAECs compared to those in HCASMCs.

Conclusions Taken together, our results suggest that ibuprofen could be an effective treatment for the development of novel DES. Its effects on migration and proliferation of HCASMCs, and induction of a differentiated phenotype, could translate into reduced rates of restenosis, whilst the lack of an effect on HCAEC migration could result in a reduced risk of late in-stent thrombosis. Further studies in animal models will be required to evaluate the performance of an ibuprofen DES *in vivo*.