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COMBINATION THERAPY IN PULMONARY HYPERTENSION

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Pulmonary hypertension (PAH) is defined as increase in mean pulmonary arterial pressure >= 25 mmHg at rest assessed by right heart catheterisation. Pulmonary arterial hypertension (PAH) is a group of patients with precapillary PH, defined by pulmonary wedge pressure <= 15 mmHg, pulmonary vascular resistance >3 Wood units in the absence of other causes of pre-capillary PH. Imbalance of three major pathways of the endothelial function (endothelin, prostacyclin and the nitric oxide pathway) has been shown to be involved in the disease process. All the drugs approved for the PAH treatment target one of these three pathway beside calcium channel blockers for reactive PAH. Combination therapy allows distinct pathways to be targeted simultaneously with additive or synergistic beneficial effect and it can be started sequentially or initially with two or three drugs. Treatment goal is to achieve a low risk status (estimated risk 1- year mortality <5%) assessed by clinical signs and symptoms, functional status, echocardiographic and haemodynamic parameters.
Majority of trials investigated sequential dual therapy versus monotherapy and only few of them investigated upfront combination dual versus monotherapy or sequential triple therapy versus dual therapy. There was only one nonrandomised trial with upfront triple therapy. Long-term studies have demonstrated that patients can benefit from both initial and sequential combination therapy.
Based on results of the published studies The European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines stated that either sequential or initial oral combination dual therapy can be used to treat patients who are considered at low or intermediate risk of clinical worsening or death. High-risk patients should receive initial combination therapy whit iv epoprostenol without delay according to latest ESC/ERS guidelines. The development of oral therapies targeting the prostacyclin pathway allows triple therapy to be implemented earlier without burden of parenteral prostanoids and one study with triple versus dual oral therapy is now ongoing. Future date are expected to help physicians to determine the optimum combinations of treatment for

different patient cohorts.