Supplementary table: Pivotal animal studies that delineated mechanisms of carcinoid heart disease.

Study	Animal model/study design	No.	Intervention/ Methods	Outcomes
Gustafsson et al[13].	Sprague-Dawley rats	48	Long term administration of subcutaneous serotonin daily for 3 months while controls were injected with saline	1. Hyperserotonemia and carcinoid syndrome developed in rats. 2. After 3 months, 6/10 rats had pathological and echocardiographic evidence of CHD 3. Normal aortic cusps of rats expressed mRNA for serotonin receptors 5-HT_{1A}, 5-HT2A,5-HT_{2B} and serotonin transporter 5-HTT indicating the direct role of serotonin in pathogenesis

				4. Histology of affected valves showed carcinoid plaque like deposits, shortened, and thickened aortic cusps
Mekonsto-Dessap et al[14].	Mice	11	Mice lacking 5-HTT and 5-HT_{1B} were generated by homologous recombination on a mixed genetic background.	1. Mice lacking 5-HTT developed marked interstitial, valvular and perivascular fibrosis in both ventricles. 2. However, Mice lacking 5-HT_{1B} receptors were no different to mice deficient in both 5-HTT and 5-HT_{1B}. Hence contribution of -HT_{1B} receptors in valvolopathy has been ruled out

				3. Echocardiogram and hemodynamics showed left ventricle (LV) dilation and decrease in LV diameter fractional shortening in 5-HTT knockout mice
Lancellotti et al[15].	White Rabbits	10	Long term oral serotonin was administered to 5 rabbits via drinking water for 16 weeks and 5 rabbits received placebo	1. Sustained hyperserotonemia was seen in experimental group 2. Moderate-severe tricuspid regurgitation (TR) developed in all serotonin treated rabbits compared to none in placebo group 3. Histological examination of experimental group showed chondroid metaplasia, carcinoid

				like plaques and thickened valvular leaflets. 4. Thus, demonstrating long term oral administration of serotonin can cause valvular heart disease in rabbits.
Droogmans et al[16].	Male Wistar rats	30	8 rats were injected with serotonin(20mg/kg) subcutaneously, 8 rats with pergolide(5mg/kg) intraperitoneally and 14 rats with vehicle only for 5 months	At 20 weeks Echocardiography showed: 1. Aortic regurgitation (AR) is more evident in serotonin (86%, P=0.0001) and in pergolide (67%, P= 0.003) compared to none in placebo. 2. Mitral regurgitation (MR) is more evident in serotonin (57%, P= 0.006) and in pergolide (67%,

				P:0.003) compared to none in placebo. 3. Pulmonary regurgitation (PR) and tricuspid regurgitation are seen both in experimental and placebo groups. However, tricuspid regurgitant area ratio was more severe in serotonin (median 26.5%; P=0.02) and pergolide animals (32%; P=0.03) compared to placebo.
Janssen et al[17].	Adult male C57BL/6J Mice	30	7 days after pulmonary artery banding (PAB), mice were treated with 14 days of 5-HT receptor antagonist (Terguride or SB204741)	1. Prolonged treatment with 5-HT receptor antagonists reduced right ventricular (RV) fibrosis and improved hemodynamics in a

				mouse model of pressure overload. 2. 5-HT2B receptor antagonists remarkably decreased collagen synthesis in RV cardiac fibroblasts, thus providing a novel therapeutic approach for heart failure.