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Abstract 14963: Isosorbide Dinitrate, With or Without Hydrazine, Does Not Reduce Wave Reflections, LV Hypertrophy or Fibrosis in HFpEF.

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Arterial wave reflections, which are increased in heart failure with preserved ejection fraction (HFpEF), impair diastolic function and promote pathologic myocardial remodeling. Organic nitrates reduce wave reflections acutely, but whether this is sustained chronically or affected by hydralazine is unknown. We randomized 44 subjects with HFpEF in a double-blinded fashion to isosorbide dinitrate (ISDN), ISDN+hydralazine (ISDN+Hydral), or placebo for 24 weeks. The primary endpoint was the change in reflection magnitude (RM, assessed with arterial tonometry and Doppler echocardiography). Secondary endpoints included the change in LV mass and fibrosis on cardiac MRI and six-minute walk (6MW) distance. ISDN reduced aortic characteristic impedance (Median baseline: 0.13 [IQR 0.12,0.17]; 3-month: 0.10 [0.06,0.17]; final: 0.09 [0.08,0.15] mmHg/mL/s,  $P=0.003$ ) and forward wave amplitude (Pf, median baseline: 48.7 [IQR 42.5,63.1], 3-month: 38.0 [25.8,49.0]; final: 40.4 [23.6,52.0] mmHg,  $P=0.04$ ), but had no effects on RM ( $P=0.64$ ). ISDN+Hydral increased RM (Median baseline: 0.37 [IQR 0.31,0.43]; 3-month: 0.35 [0.27,0.37]; final: 0.45 [0.41,0.58],  $P=0.03$ ), reduced 6MW distance (Median baseline: 398.7 [IQR 297.0,432.7]; final: 300.0 [122.0,370.7] meters,  $P=0.022$ ), and increased native myocardial T1 (Median baseline: 1002 [IQR 974,1006]; final: 1060 [1034.5,1121.5],  $P=0.021$ ), suggesting increased fibrosis. A higher proportion of subjects experienced adverse events with active therapy (ISDN=61.5%, ISDN+Hydral=60%; Placebo=12.5%;  $P=0.007$ ). Long-term administration of ISDN, with or without hydralazine, does not exert beneficial effects on RM, LV remodeling, or submaximal exercise and is poorly tolerated. The combination of ISDN+Hydral has deleterious effects on RM, interstitial remodeling, and submaximal exercise. Our findings do not support the routine use of these vasodilators in HFpEF.

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