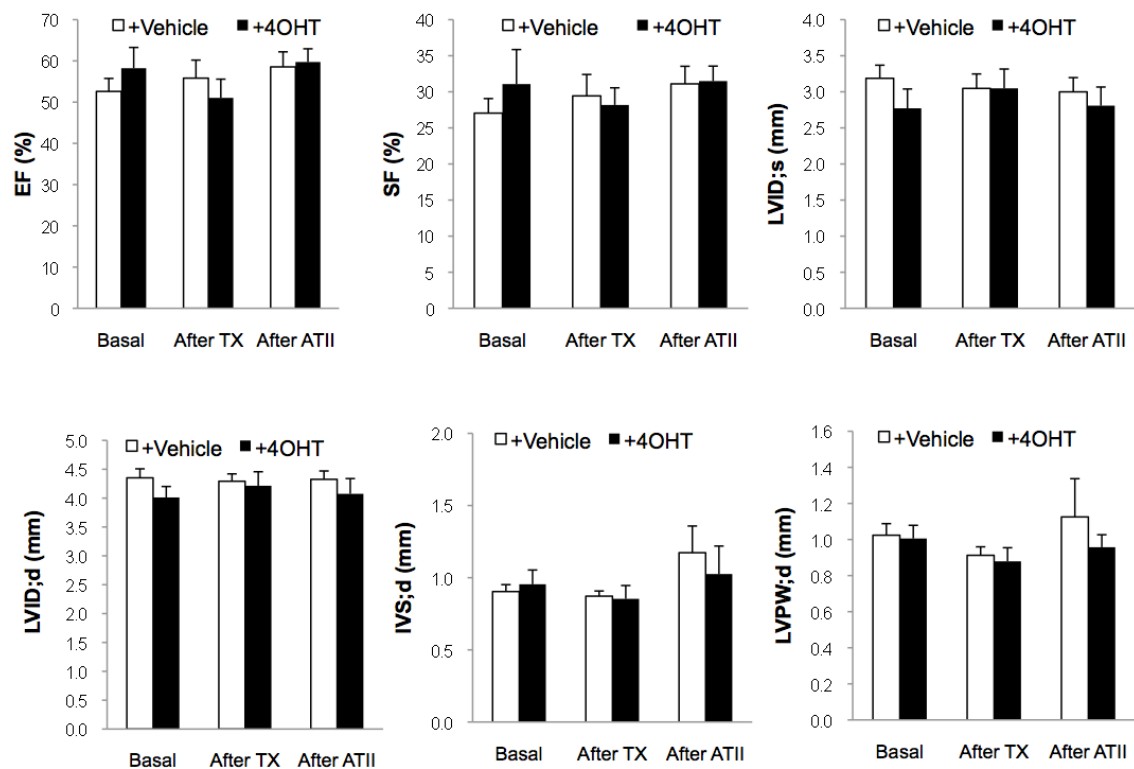


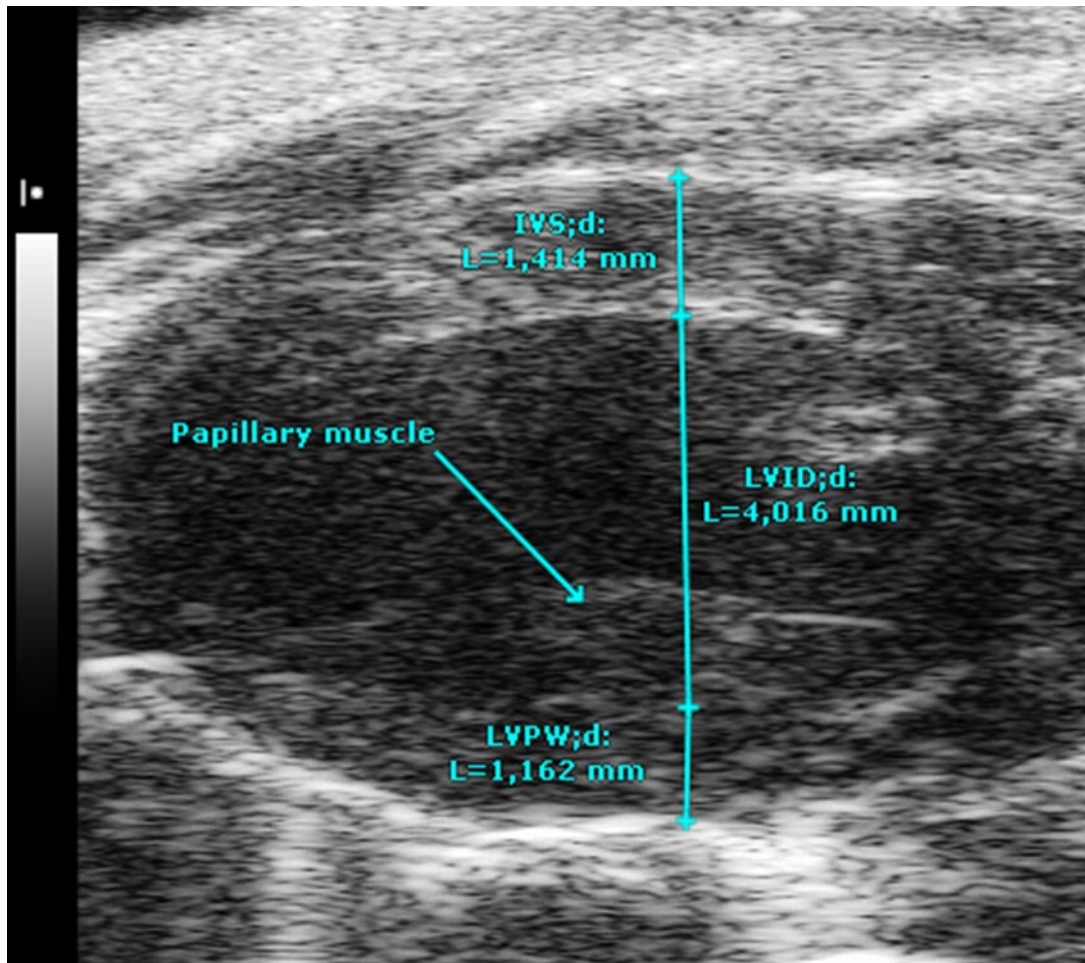
SUPPLEMENTAL MATERIAL

Targeting γ -secretases protects against angiotensin II-induced cardiac hypertrophy

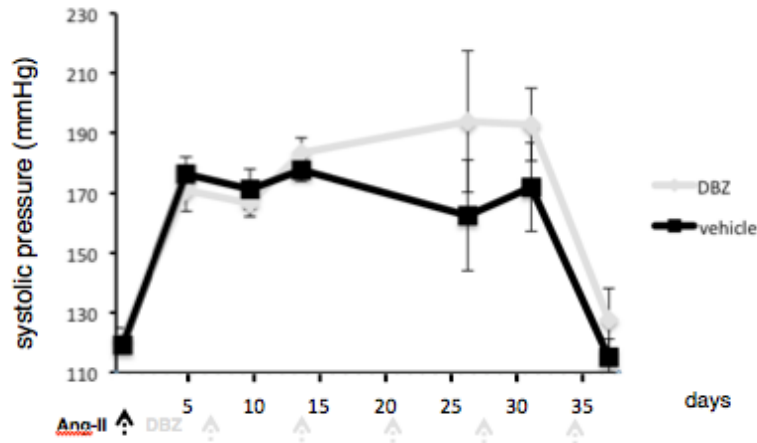
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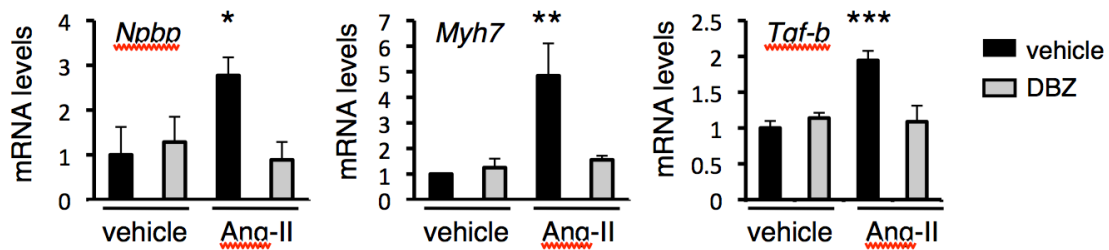
Supplementary Fig. 1. Cardiac function is unaltered by genetic targeting of the γ -secretase complex. Cardiac parameters were evaluated in *Psen^{fl};Psen2^{-/-};Cre^{ERT2/ERT2}* mice by transthoracic echocardiography in B- and M-mode. Echocardiography was carried out before any treatment (Basal), after two injections (separated by 4 days) with vehicle or 4-OHT to induce Cre recombinase expression (TX), and after 15 days of Ang-II (ATII) subcutaneous osmotic pump implantation, as indicated. Graphs show ejection fraction (EF), fractional shortening (FS), and parameters measured to calculate left ventricular mass: internal diameter (LVID), posterior wall (LVPW), and interventricular septum thickness (IVS) measured at systole (s) and diastole (d). All parameters were normalized to tibia length and animal weight, and results are shown as mean \pm SEM.



Supplementary Figure 2. Example to follow supplementary videos. Representative long-axis B-mode transthoracic echocardiography images of *Psen1^{fl};Psen2^{-/-};Cre^{ERT2/ERT2}* mice . Blue bars show interventricular septum thickness (IVS), left ventricular internal diameter and left ventricular posterior wall (LVPW) measured at systole (s). For clarity papillary muscle is also indicated. used for measurements.



Supplementary Fig. 3. Systolic pressure is unaltered by pharmacological targeting of the γ -secretase complex. Systolic blood pressure in vehicle- (n=9) or DBZ-treated (n=8) mice. The dotted black arrow indicates the time of Ang-II pump implantation and dotted grey arrows indicate the first day of four consecutive days of injections with the γ -secretase inhibitor (DBZ) or vehicle.



Supplementary Fig. 4. DBZ impaired the expression of hypertrophic genes in NkL-TAg cells. qPCR analysis of the indicated genes in NkL-TAg cells treated with Ang-II and/or DBZ for 24h (n=3 per group). *** p<0.001; **p<0.01; *p<0.05.

	<u>Age (y)</u>	<u>SBP (mm Hg)</u>	<u>DBP (mm Hg)</u>	<u>LVMI (g/m²)</u>	<u>RWT</u>	<u>Treatment</u>
non-LVH	68	143	87	103.58	0.40	D/ACEI-ARA
	69	152	93	124.44	0.41	D/ACEI-ARA
	73	145	91	128.50	0.39	D/BB-AB/CCB
	70	140	92	94.09	0.38	D/CCB
	70	155	95	94.55	0.40	BB-AB/CCB/ACEI-ARA
Mean ± SD	70 ± 1.87	147 ± 6.28	91.6 ± 2.97	109.03 ± 16.42	0.39 ± 0.01	
LVH	66*	139	93	172.85	0.46	D/CCB/ACEI-ARA
	73*	145	91	142.55	0.44	BB-AB/CCB
	75*	151	90	154.56	0.45	D/CCB/ACEI-ARA
	61*	149	99	141.70	0.43	D/ACEI-ARA
	61**	148	88	140.86	0.41	D/BB-AB/CCB
Mean±SD	67.2 ± 6.57	146.4 ± 4.67	92.2 ± 4.21	144.9 ± 6.46	0.43 ± 0.01	

Supplementary Table 1. Demographic, hemodynamic, echocardiographic and treatments parameters in hypertensive male patients. SBP means systolic blood pressure; DBP, diastolic BP; LVMI, left ventricular mass index; RWT, relative wall thickness; LVH, LV hypertrophy; D, diuretics; BB, beta-blockers; AB, alpha-blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARA, angiotensin receptor antagonists. * The quantitative criteria to diagnose LVH either concentric (*) or eccentric (**) were the criteria recommended by Lang RM et al. J Am Soc Echocardiography 2005;18:1440-1463. SD, standard deviation.