cGMP inhibits hypertrophy, decreases fibrosis, and protects against cardiac ischemia-reperfusion (I/R) injury. Gene-targeting studies have not defined a clear role for its major downstream effector, cGMP-dependent protein kinase I (cGKI), in cardiac hypertrophy, but do implicate cGMP-cGKI signaling in fibrosis and I/R injury. No direct cGKI activators have advanced to clinical trials, whereas cardiac trials of agents that modulate cGMP via particulate or soluble guanylyl cyclases (GCs) and phosphodiesterase 5 (PDE5) are ongoing. Here we review concerns arising from preclinical and clinical studies that question whether targeting the cGMP pathway remains an encouraging concept for management of heart dysfunction. So far, trial results for GC modulators are inconclusive, and sildenafil, a PDE5 inhibitor, although cardioprotective in mouse models, has not shown positive clinical results. Preclinical cardioprotection observed for sildenafil may result from inhibition of PDE5 in non-cardiomyocytes or off-target effects, possibly on PDE1C. On the basis of such mechanistic considerations, re-evaluation of the cellular localization of drug target(s) and intervention protocols for cGMP-elevating agents may be needed.