Introduction Medications that target and downregulate the immune system are utilized for the prevention and treatment of a variety of conditions, including neoplasms, autoimmune diseases, and acute rejection after solid organ transplantation (1).In a rat model of myocardial infarction, everolimus improved postinfarct remodeling (72) although in the recently published CLEVER–ACS trial of patients with myocardial infarction, there everolimus treatment had no effect on myocardial remodeling (73).Herein, we focus on the cardiovascular effects and mechanistic underpinnings of calcineurin inhibitors (CNI), mammalian target of rapamycin (mTOR) inhibitors, and purine synthesis inhibitors (Figure Hypertrophy and fibrosis Cardiac hypertrophy is a feature of adverse cardiac remodeling that may be driven by genetic or acquired factors.In addition to the well described increased risk of infection and malignancy in chronically immunosuppressed patients, many of these agents exhibit direct effects on the cardiovascular system including risk of left ventricular (LV) hypertrophy, myocardial fibrosis, arrhythmia, hypertension, dyslipidemia, and coronary atherosclerosis (4).Calcineurin inhibitors Calcineurin, a calcium and calmodulin–dependent phosphatase, plays a pivotal role in cardiac hypertrophy by translocating to the nucleus and dephosphorylating NFAT, allowing it to transcribe genes to activate hypertrophy in cardiomyocytes.In early animal experiments, CsA successfully prevented or attenuated cardiac hypertrophy in mice overexpressing contractile elements (10, 29), genetic predispositions to hypertrophy (19), and treatment with exogenous chemical signals promoting hypertrophy (11, 15, 60).In animal models of hypertrophy induced by phenylephrine stimulation, spontaneously hypertensive rats, or aortic banding, tacrolimus treatment had variable effects, with exacerbation or amelioration of the hypertrophic phenotype (16, 38, 61, 62).Tacrolimus binds to FK506–binding protein (FKBP12) to inhibit calcineurin activity driving reduced NFAT–mediated transcription of hypertrophic genes.mTOR inhibitors mTOR inhibitors, such as sirolimus and everolimus, inhibit mammalian target of rapamycin complex I, thereby inhibiting downstream pathways driving cell growth, proliferation, and survival.Cellular data highlight that the increase in LV mass may be driven primarily by CNI–induced increase in fibrosis and collagen deposition rather than cardiomyocyte remodeling.However, everolimus binding to FKBP–12 is ~3–fold weaker than that of sirolimus, leading to significant differences in inhibition of mTORC2 activation and downstream effects (68, 69).Sirolimus has been shown to reduce cardiac hypertrophy and fibrosis in animal models of pressure overload, uremia, and adriamycin induced cardiomyopathy (42, 43, 71).Similar data of increased collagen deposition in response to tacrolimus treatment was observed in human induced pluripotent stem cellderived cardiac organoids treated with tacrolimus (65).This class of drugs has garnered significant interest in solid organ transplantation owing to salutary effects on renal function, allograft vasculopathy and malignancy risk (70).Hypertrophy is frequently seen in association with diastolic dysfunction and represents an important marker for adverse remodeling (5, 6).Cyclosporine (CsA) binds to cyclophilin A, forming a complex with high affinity for calcineurin, which in turn inhibits its .nuclear translocation.Tacrolimus has also yielded mixed results