Data Supplement 1. Genetics Table

Study name	Author (citation)	Aim of study	Study design	Study size	Patient population	Endpoints	Results	Comments
Quality of life and psychological distress in hypertrophic cardiomyopathy mutation carriers: a cross-sectional cohort study	Christiaans, I, van Langen IR, Birnie E, Bonsel GJ, Wilde AAM, Smets EMA. Amercian journal of Medical Genetics; 2009:149A:602-612 (1)	To determine the quality of life and psychological distress in HCM mutation carriers.	Cross sectional cohort study	228 patients who underwent genetic testing for HCM mutation	Carriers of HCM mutations. 49.1% men, 88.7% with children. Study group divided between those with known HCM and those with unknown clinical status, in whom genotype would be predictive (n=123). Among those with predictive genotype: 43% were men and 57% were women, with 76.4% had children.	Quality of life and psychological distress assessed. Mutation carrier responses were compared to the general population.	Overall scores of quality of life were not different from the general population. Among those with overt HCM, quality of life and distress were worst than general population. Predictive genetic testing did not cause worse psychological test scores than those in the general population. Among those whose DNA testing indicated they did not carry a HCM mutation, quality of life scores were better than general population.	This was the first study to show that there was no psychologic harm caused by predictive genetic testing in HCM.
Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy	Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. N Engl J Med. 1992 Apr 23;326(17):1108-14 (2)	To assess the role of *MYH7* mutations in unrelated families with HCM	Genetic analyses of *MYH7*	25 unrelated HCM probands and ~250 family members	Familial HCM of European descent.	Identification of pathogenic mutations.	Dominant missense mutations in *MYH7* accounted for HCM in 12/25 families, indicating this gene accounts for approximately 50% of familial HCM. Mutations allowed identification of individuals at risk for developing HCM. Different mutations did not appreciably alter the clinical manifestations of familial HCM.	Different missense mutations in the β cardiac myosin heavy-chain gene can be identified in approximately 50% of families with HCM. The study authors suggest the precise definition of the disease-causing mutation can provide important prognostic information about affected members.
Comprehensive analysis of the beta-myosin heavy chain gene in 389 unrelated patients with hypertrophic cardiomyopathy	Van Driest SL, Jaeger MA, Ommen SR, Will ML, Gersh BJ, Tajik AJ, Ackerman MJ. J Am Coll Cardiol. 2004 Aug 4;44(3):602-10. (3)	Assessment of the prevalence of *MYH7* mutations in an unselected HCM cohort	DNA sequence analyses	389 HCM patients	Unrelated HCM patients with familial or sporadic disease referred to a tertiary center.	Identification of pathogenic mutations.	58 patients (15%) had 40 different mutations in *MYH7*. HCM patients with *MYH7* compared to HCM patients without *MYH7* mutations, were younger at diagnosis (32.9 vs. 42.7 years, respectively, p=0.0002), had more hypertrophy (LV wall thickness of 24.2 vs. 21.1 mm, respectively, p=.0009), and more frequently underwent myectomy (60% vs. 38%, respectively, p = 0.002). HCM patients with *MYH7* mutations compared to HCM patients without *MYH7* mutations more often had a family history of HCM (43% vs. 29%, respectively, p=.006).	Mutations were identified using indirect methods that are less sensitive than contemporary approaches, such as DNA sequencing. This is likely to account for the lower prevalence of *MYH7* mutations than is currently found by contemporary clinical and research mutation tests.

Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy	Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, Spirito P, Matsumoir A, Moravec CS, Seidman JG and Seidman CE. NEJM 1995; 332:1058-65 (4)	To determine the role of troponin T and alpha tropomyosin mutations in HCM	DNA sequence analyses	127 unrelated HCM probands	Probands with familial HCM included 14 from Europe, 10 from North America and 1 each from South America, Africa and India. 100 HCM probands without family histories had diverse racial and ethnic origins.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant mutations in cardiac troponin T account for ~15% of familial HCM; dominant mutations in alpha-tropomysoin account for ~3% of HCM.	The high detection rate of troponin T mutations may be due to the referral-center population studied. Subsequent analyses indicate troponin T mutations account for somewhat less (10%) of HCM.
Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy	Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, Kristinsson A, Roberts R, Sole M, Maron BJ, Seidman JG, Seidman CE. N Engl J Med. 1998 Apr 30;338(18):1248-57. (5)	To determine the spectrum of myosin binding protein C mutations and associated clinical features	DNA Sequence analyses	Unrelated HCM probands and 574 family members	Single center analyses of familial HCM.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant missense and trunation mutations in cardiac myosin binding protein C account for ~50% of familial HCM. Only 58% of adults <50 years of age with a cardiac myosin-binding protein C mutation had clinical manifestations of HCM. Disease penetrance remained incomplete through the age of 60 years.	This was the first study to show myosin binding protein C mutations can delay clinical expression of HCM. This study was significant in that clinical evaluations of family members at risk for HCM must continue throughout life, unless genetic status is ascertained.
Sporadic hypertrophic cardiomyopathy due to de novo myosin mutations	Watkins H, Thierfelder L, Hwang DS, McKenna W, Seidman JG, Seidman CE. J Clin Invest. 1992 Nov;90(5):1666-71. (6)	To determine if isolated cases of HCM, like familial HCM are due to gene mutations.	Single center cohort genetic study	7 patients	Unrelated patients with sporadic HCM.	Identification of pathogenic mutations.	Mutations in the beta cardiac MHC gene were identified in two probands with sporadic disease. In each case, the parents were neither clinically nor genetically affected, indicating mutations arose de novo. Transmission of the mutation and disease to an offspring occurred in one pedigree, predicting these are germline mutations.	This study demonstrated de novo mutations account for some instances of sporadic HCM and these mutations can be transmitted to children, indicating genetic testing is warranted in patients with sporadic disease.
Shared genetic causes of cardiac hypertrophy in children and adults	Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, Towbin JA, Seidman JG, Seidman CE. N Engl J Med. 2008 May 1;358(18):1899-908. Epub 2008 Apr 9 (7)	To determine if idiopathic cardiac hypertrophy in childhood that occurs without a family history of cardiomyopathy has a shared genetic etiology with HCM.	Genetic study of children with idiopathic hypertrophy	84 patients	63 boys/ 21 girls diagnosed before 15 years of age (mean [+/-SD] age, 6.99+/-6.12 years).	Identification of pathogenic mutations and assessment of mutation in family members.	Pathogenic mutations were identified 25 of 51 affected children without family histories of cardiomyopathy and in 21 of 33 affected children with familial HCM. Among 11 of the 25 children with presumed sporadic disease, 4 cases had new mutations and 7cases had unrecognized inherited mutations.	This study showed mutations in HCM genes account for ~50% of cases of pediatric onset of idiopathic hypertrophy, despite substantially different clinical presentation. In 1/3 of cases, de novo mutations were found. Genetic testing of childhood-onset hypertrophy can help define cause and aid in family evaluations.

Glycogen storage diseases presenting as hypertrophic cardiomyopathy	Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. N Engl J Med. 2005 Jan 27;352(4):362-72. (8)	To determine the genetic causes of HCM with atypical features.	Cohort genetic study of patients with atypical HCM	55 patients	Unrelated HCM patients with massive hypertrophy, early presentation, absent family history, or concurrent electrophysiologic abnormalities.	Identification of pathogenic mutations and assessment of clinical features associated with different genotypes.	Mutations in *LAMP2* and *PRKAG2* cause hypertrophy with additional features. Clinical features associated with *PRKAG2* mutations included electrophysiological abnormalities (pre-excitation and progressive conduction system disease). Clinical manifestations of *LAMP2* mutations included male sex, severe hypertrophy, early onset (at 8 to 17 years of age), ventricular preexcitation, and asymptomatic elevations of two serum proteins.	This study showed that *LAMP2* or *PRKAG2* mutations resembles HCM but are distinguished by electrophysiological abnormalities, and for *LAMP2* mutations, extra-cardiac manifestations. The clinical courses associated with these mutations are distinct from HCM. Gene-based diagnosis can distinguish between HCM and these disorders. This information is helpful to counsel patients and to devise appropriate management strategies.
Preclinical diagnosis of familial hypertrophic cardiomyopathy by genetic analysis of blood lymphocytes	Rosenzweig A, Watkins H, Hwang DS, Miri M, McKenna W, Traill TA, Seidman JG, Seidman CE. N Engl J Med. 1991 Dec 19;325(25):1753-60 (9)	To determine if genetic information identifies mutation carriers and to define preclinical manifestations of HCM.	Single center family study	29 family members of index HCM patient	15 adult family members and 14 offspring (ages 1- 20 years).	Definition of genotype and clinical features of all study subjects.	In 15 adult relatives there was perfect agreement between genotype and the clinical diagnosis (8 affected and 7 not affected). Clinical analysis of the 14 offspring of affected adults identified 1 child with echocardiographic findings diagnostic of HCM. However, genetic analyses showed 6 other children had also inherited the mutation. Some genotype positive children without LVH had EKG abnormalities, indicating that electrophysiologic manifestations precede LVH in HCM.	This study shows that knowledge of the genetic cause for HCM in an index patient allows preclinical diagnosis of mutation carriers, and identification of relatives who have no risk of developing HCM. Genotype information can precisely define individuals who warrant serial clinical evaluations for HCM.
Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy	Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, Seidman CE, Solomon SD. Circulation. 2002 Jun 25;105(25):2992-7 (10)	To determine the pre-clinical phenotypes in carries of HCM mutations who do not exhibit LVH.	Cohort study	72 patients	36 subjects with HCM mutations; 18 without LVH (genotype+/LVH-) and 18 with LVH (genotype+/LVH+). Controls = 36 age/gender matched individuals without an HCM mutation.	LV function using 2-D echocardiography with Doppler tissue imaging.	LVEF was significantly higher in both genotype (+) groups versus control subjects. Mean early diastolic myocardial velocities (Ea) were significantly lower in both genotype (+) subgroups, irrespective of LVH.	This study defines the earliest clinical manifestations of HCM. Abnormalities of diastolic function were shown to precede the development of LVH in individuals with HCM mutations. This finding supports the rationale for serial evaluation of genotype + individuals, to enable early detection of the emergence of HCM.
A DNA resequencing array for pathogenic mutation detection in hypertrophic cardiomyopathy	Fokstuen S, Lyle R, Munoz A, Gehrig C, Lerch R, Perrot A, Osterziel KJ, Geier C, Beghetti M, Mach F, Sztajzel J, Sigwart U, Antonarakis SE, Blouin JL. Hum Mutat. 2008 Jun;29(6):879-85. (11)	To define gene mutations in familial and sporadic HCM using contemporary sequencing techniques.	Cohort study from a single center	38 patients	17 index patients with familial HCM; 21 with sporadic HCM.	12 genes clearly implicated in HCM were sequenced in all patients. (Genes = *MYH7, MYBPC3, TNNT2, TPM1, TNNI3, MYL3, MYL2, CSRP3, PLN, ACTC, TNNC1,* and *PRKAG2*).	Pathogenic mutations were identified in 60% (10/17) of familial HCM and 10% of sporadic cases (2/21).	Contemporary DNA sequencing strategies can detect HCM mutations in ~60% of patients with familial disease and 10% of subjects with sporadic disease.

Diastolic dysfunction without left ventricular hypertrophy is an early finding in children with hypertrophic cardiomyopathy-causing mutations in the beta-myosin heavy chain, alpha-tropomyosin, and myosin-binding protein C genes	Poutanen T, Tikanoja T, Jääskeläinen P, Jokinen E, Silvast A, Laakso M, Kuusisto J. Am Heart J. 2006 Mar;151(3):725.e1-725.e9. (12)	To compare biomarkers, LVH and diastolic function in children with a HCM mutation (genotype positive) versus healthy control children	Cohort study from a single center	53 children	27 children with a HCM mutation and 28 controls (mutation negative).	Clinical analyses of 27 children with HCM mutations (genotype +) compared to age-matched children without mutations.	Genotype positive children had thicker septal measurements compared to the control children (P=.004), but only 3 (11%) genotype positive children fulfilled criteria for body surface area adjusted maximal LV thickness of healthy children. However all genotype positive children had prolonged is ovolumetric relaxation time, increased left atrial volume, or increased levels of *NT-proANP.*	This study confirms LVH is a late manifestation of HCM. Children with HCM mutations have other clinical abnormalities including diastolic dysfunction.
Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy	Olivotto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, Ommen SR, Theis JL, Vaubel RA, Re F, Armentano C, Poggesi C, Torricelli F, Cecchi F. Mayo Clin Proc. 2008 Jun;83(6):630-8. (13)	Assessment of clinical course in patients with a known mutation versus patients in whom no mutation is defined.	Cohort study from a single center	203 HCM patients	87 patients with a mutation and 126 patients without a mutation. 8 myofilament genes were sequenced (*MYH7, MYBPC3, TNNT2, TPM1, TNNI3, MYL3, MYL2, ACTC*) and clinical course assessed over a mean of 4 years.	Cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV.	Despite similar baseline features, patients with HCM mutations had increased risk of the combined endpoints of cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV compared with the patients without mutations. Mutation positive patients also had greater LV dysfunction (systolic and diastolic abnormalities) in comparison to mutation negative patients.	This study showed a direct relationship between a positive genotype and outcomes in HCM. Unlike patients in whom no mutation was identified, those with a sarcomere gene mutation had a significantly poorer prognosis.
Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counseling	Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. J Med Genet. 2005 Oct;42(10):e59 (14)	To compare the clinical phenotypes in carries of one or multiple HCM mutations.	Cohort genetic and clinical study	80 unrelated HCM index patients and family members	19 index patients with one mutation, 4 index patients and 11 family members with >1 mutation.	Clinical manifestations and course (sudden death, transplant, etc) in single and multiple mutation subjects.	5% of the HCM cohort had >1 mutation. Six of 14 (43%) of affected individuals with >1 HCM mutation had sudden cardiac death vs. 10 of 55 (18%) in affected individuals with 1 mutation. There was an increased LVH in patients with >1 mutations (mean: 30.7 mm) vs. 24.4 mm in patients with 1 mutation.	Multiple gene mutations cause more severe HCM possible due to a ‘‘double dose’’ effect.

DNA indicates deoxyribonucleic acid; EKG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; and SD, sudden death.

Data Supplement 2. Invasive Therapies Table

Study name	Author (citation)	Aim of study	Study design	Study size	Patient population	Endpoints	Results	Comments
Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation.	van der Lee C, Scholzel, ten Berg JM, et al. Am J Cardiol. 2008;101:1315-20. (15)	To assess outcomes after septal ablation	Multiple center retrospective review of consecutive patients	131 patients	HCM patients treated with septal ablation	Complications (in-hospital; follow-up); unsuccessful therapy;	Ablation success in 90%; complications in 15% including death in 3.8%	Long-term success was related to procedural volume
Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes.	Firoozi S, Elliott PM, Sharma S, et al. Eur Heart J. 2002;23:1617-24. (16)	To compare subjective outcomes among HCM patients undergoing surgical myectomy and septal ablation	Single center retrospective review	44 patients	24 HCM patients treated with surgical myectomy; 20 HCM patients treated with septal ablation	Echocardiographic gradient; NYHA class; Cardiopulmonary exercise testing;	Gradient and NYHA improvements were similar between the 2 treatment modalities. Objective exercise parameters improved more with surgical myectomy	
Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy.	Ommen SR, Maron BJ, Olivotto I, et al. Journal of Am Coll Cardiol. 2005;46:470-6. (17)	To determine impact of surgical myectomy on long-term survival	Multiple center retrospective review of concurrent patient cohorts	1337 patients	289 HCM patients treated with surgical myectomy; 228 patients with obstructive HCM treated pharmacologically; 820 nonobstructive HCM patients	Overall and cardiac survival	1, 5, and 10 year survival (98%, 96%, and 83%, respectively) after surgical myectomy is equivalent to healthy age and gender matched population. Overall and cardiac survival superior to that of obstructive patients not offered operation.	30-day mortality = 0.8%. Annualized cardiac mortality rate 0.5% per year
Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score.	Ralph-Edwards A, Woo A, McCrindle BW, et al. Journal of Thoracic & Cardiovascular Surgery. 2005;129:351-8. (18)	Review of early outcomes after surgical myectomy or septal ablation	Single center retrospective review of concurrent patient cohorts	150 patients	90 HCM patients treated with surgical myectomy; 60 HCM patients treated with septal ablation	Survival, NYHA class, echocardiographic gradient	Superior 4 y survival, gradient reduction, and NYHA class improvement were observed in the myectomy patients after adjusting for baseline differences	
Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy.	Smedira NG, Lytle BW, Lever HM, et al. Ann Thorac Surg. 2008;85:127-33. (19)	To assess effectiveness and risks of surgical myectomy	Single center retrospective review of consecutive patients	323 patients	HCM patients treated with surgical myectomy	Echocardiographic gradient; NYHA class; need for reintervention for HCM	Gradient decreased from 68 mmHg to 17 mmHg ; no in-hospital mortality; freedom from reintervention at 8 y was 92%;;	

Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy.	Sorajja P, Valeti U, Nishimura RA, et al. Curculation. 2008;118:131-9. (20)	Assess outcomes after septal ablation	Single center retrospective review	138 patients	HCM patients treated with septal ablation	Gradient, survival, complications	Relief of LVOT gradient 83% (p<0.001);1.4% procedural death rate with ablation; 4 y overall survival = 88%; 4 y survival free from NYHA class III to IV symptoms was 76% after ablation	Posthoc Analysis: among patients <65 years of age, survival free of symptoms was better with myectomy
Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy.	Woo A, Williams WG, Choi R et al. Circulation. 2005;111:2033-41. (21)	Determine clinical and echocardiographic factors associated with long-term morbidity and mortality after surgical myectomy	Single center retrospective review of consecutive patients	338 patients	HCM patients treated with surgical myectomy	Mortality, predictors of mortality, NYHA class	Early post-op mortality = 1.5%, 10 yr survival = 83+/-3%; Improvement to NYHA class I to II observed in 83%	Predictors of major CV events were age, female sex, preoperative AF, concomitant CABG and preoperative left atrial size
Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy. The Baylor and Medical University of South Carolina experience, 1996 to 2007.	Fernandes VL, Nielsen C, Nagueh SF, et al. JACC Cardiovasc Interv. 2008;1:561-70. (22)	Determine long-term outcome after alcohol septal ablation	Retrospective review of consecutive patients	629 patients	HCM patients treated with alcohol septal ablation	Mortality, complications, repeat invasive therapy for HCM pacemaker requirement, and NYHA Class	Early mortality = 1%, 1, 5, 8 y survival (97%, 92%, 89%, respectively), Permanent pacemaker required in 8.2%. Mean NYHA class at 4-5 y decreased from 2.8 +/- 0.6 to 1.2 +/--0.5 (p<0.001)= 1.2	
Transcoronary ablation of septal hypertrophy for hypertrophic obstructive cardiomyopathy: feasibility, clinical benefit, and short term results in elderly patients.	Gietzen FH, Leuner CJ, Obergassel L, Strunk-Mueller C, Kuhn H. Heart. 2004; 90:638-44. (23)	Evaluate symptomatic and hemodynamic results of septal ablation in elderly patients	Single center retrospective review of consecutive patients	157 patients	HCM patients treated with septal ablation. Group I <60 years of age, Group II ≥60 years of age.	Mortality, gradient, complications, NYHA class	Early mortality similar between groups. Total mortality 3.8% in Group I vs. 9.1% in Group II. Similar improvement in symptoms and exercise time. Patients ≥60 years of age more likely to have persistent atrioventricular heart block (5% vs. 17%, p=0.015. NYHA class improved from 2.7 to 1.4 in Group I and 3.0 to 1.7 in Group II.	
Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience.	Kuhn H, Lawrenz T, Lieder F, et al. Clin Res Cardiol. 2008;97:234-43. (24)	Determine impact of septal ablation on survival	Single center retrospective review of consecutive patients	644 patients	HCM patients treated with septal ablation	Mortality (early and late)	Early mortality = 1.2%, annual mortality = 3.2% per year	Early and late mortality improved after converting to low alcohol dosing

Long-Term Outcomes in High-Risk Symptomatic Patients With Hypertrophic Cardiomyopathy Undergoing Alcohol Septal Ablation.	Kwon D.H., Kapadia S.R., Tuzcu E.M., et al. J Am Coll Cardiol Intv. 2008; 1:432-8. (25)	Assess outcomes after septal ablation in high-risk patients	Single center retrospective review	55 patients	HCM patients at high risk for cardiac surgery treated with septal ablation	Gradient, quality of life, NYHA class, mortality	Gradient and quality of life improved at 3 mo and sustained through 1 y. Reduction in number of patients with NYHA functional class ≥3 (93% NYHA functional class >2). Early mortality = 2%, 1, 5, 10 y survival (96%, 87%, 76%);	
Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy.	Nagueh SF, Ommen SR, Lakkis NM, et al. J Am Coll Cardiol. 2001;38:1701-6. (26)	Compare hemodynamic efficacy of surgical myectomy and septal ablation	Multicenter retrospective case-control comparison	82 patients	41 HCM patients treated with septal ablation; 41 age and gradient matched HCM patients treated with surgical myectomy	Gradient, NYHA class, exercise capacity	At 1 y after procedure, improvements in gradient, symptoms and exercise capacity were similar between the 2 groups	
Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery.	Qin JX, Shiota T, Lever HM, et al. J Am Coll Cardiol. 2001;38:1994-2000. (27)	Evaluate results of surgical myectomy as compared to septal ablation	Single center retrospective review	51 patients	25 HCM patients treated with septal ablation; 26 HCM patients treated with surgical myectomy	Gradient, NYHA class	Gradient reduction more robust with surgery; NYHA improvements similar	Ablation patients in this study were on average 15 y older than myectomy patients
Updated meta-analysis of septal alcohol ablating versus myectomy for hypertrophic cardiomyopathy.	Agarwal S, Tuzcu EM, Desai MY, Smedira N, Lever HM, Lytle BW, Kapadia SR. J Am Coll Cardiol 2010;55:823-34. (28)	Compare outcomes of HCM patients undergoing surgical myectomy with septal ablation	Meta-analysis	12 published studies	HCM patients treated with either surgical myectomy or septal ablation	Mortality, complications, NYHA class, gradient,	No differences in mortality, NYHA class, ventricular arrhythmia, or need for reintervention. Ablation patients had higher residual gradient and rate of advanced conduction abnormalities	
Meta-analysis of septal reduction therapies for obstructive hypertrophic cardiomyopathy. Comparative roles of overall mortality and sudden cardiac death after treatment.	Leonardi RA, Kransdorf EP, Simel DL, Wang A. Circ Cardiovasc Interv 2010;3:97-104. (29)	Compare outcomes of HCM patients undergoing surgical myectomy with septal ablation	Meta-analysis	27 published studies	HCM patients treated with either surgical myectomy or septal ablation	Survival and rate of SCD	No differences were observed between the treatment strategies in terms of overall, cardiac or sudden death related survival	

CABG indicates coronary artery bypass graft; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; and SCD, sudden cardiac death.

Data Supplement 3. Pacing Table

Study name	Author (citation)	Aim of study	Study design	Study size	Patient population	Endpoints	Results	Comments
Functional assessment of patients treated with permanent dual-chamber pacing as a primary treatment for hypertrophic cardiomyopathy	McDonald, K, McWilliams, E, O'Keefe, B, Maurer, B. European Heart Journal. 1988;9:893-398 (30)	To determine the improvement in objective exercise capacity in patients with hypertrophic cardiomyopathy undergoing DDD pacing	Cohort 2 center trial - DDD pacemaker implanted in all patients	11 patients (mean age 50 +/- 12 y)	Eleven selected patients with obstructive HCM and severe symptoms refractory to drug therapy studied at 2 centers who underwent initial implantation of a DDD pacemakers.	Symptoms, NYHA class and exercise time	Within 1 week, there was an improvement in NYHA class in all patients. The exercise duration increased from 7.7 to 11.5 min. In 5 patients at a follow-up of 3 mo to 1y, there was an increase in exercise time from 6.2 to 8.8 min.	One of the first studies which showed an improvement in exercise time during continuous DDD pacing.
Effects of dual-chamber pacing in hypertrophic cardiomyopathy	Jeanrenaud, X, Goy, J, Kappenberger, L. Lancet.1992;339:1318-1323 (31)	To determine the effects of acute and long-term dual-chamber pacing in patients with hypertrophic cardiomyopathy.	Cohort series. Acute pacing study and long-term implantation of a dual-chamber pacemaker.	13 patients with acute study and 8 patients with follow-up (age 56 +- 14 y)	Selected patients with obstructive HCM and severe symptoms refractory to drug therapy	NYHA class, outflow tract gradient.	At a follow-up of 14 +/- 11 mo, NYHA class had decreased from III to II in terms of dyspnea. Outflow tract gradient had decreased from 67 +/- 42 to 17 +/- 10 mmHg. When the pacemaker was turned off at follow-up, the gradient was 31 +/- 36 mmHg.	This study showed that synchronized and ventricular pacing in at an optimal AV interval does reduce intraventricular pressure gradient at the time of acute study. There is a long-term drop in pressure gradient during chronic pacing with improvement in functional tolerance.
Long-term results of dual chamber pacing in obstructive hypertrophic cardiomyopathy: evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy	Fananapazir, L, Epstein ND, Curiel, RV, Panza JA, Tripodi, D, McAreavey D. Circulation. 1994:90:2731-2742 (32)	To determine the intermediate term outcome of DDD pacing in patients with HCM.	Cohort single center trial - implant DDD pacemakers in all patients	84 patients (mean age 49 +/- 16 y)	Consecutive patients with obstructive HCM and severe symptoms refractory to drug therapy referred to a single center	Symptoms, NYHA class, LVOT gradient, LVH	At a mean follow-up of 2.3 +/- 0.8 y, there was improvement in NYHA Class (3.2 +/- 0.5 to 1.6 +/- 0.6, p<.0001). The LVOT gradient decreased from 100 +/- 47 mmHg to 29 +/- 34 mmHg - p < .01. A subset of patients had reversal of LV wall thickness.	The high success rate of DDD pacing in this cohort trial has not been replicated in subsequent randomized pacing trials.
DDD pacing in hypertrophic cardiomyopathy: A multicentre clinical experience	Slade, A, Sadoul, N, Shapiro, L, Chojnowska, L, Simon, J, Saumarez, R, Dodinot, B, Camm, A, McKenna, W, Aliot, E. Heart.1996;75:44-49 (33)	To determine the outcome of DDD pacing in patients with hypertrophic cardiomyopathy.	Cohort multicentre trial. Implant DDD pacemaker in all patients.	56 patients from 4 centers,(mean age 48 +/- 18 y old)	Selected patients with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA Class, LVOT gradient	Forty-four out of 53 patients had an improvement in functional class. At a mean follow-up of 11 +/- 11 mo, there was a reduction in gradient from 78 +/- 31 to 36 +/- 25 mmHg.	There was symptomatic improvement in the majority of patients. However, there was no correlation between the magnitude of the gradient drop and the functional improvement. This is another study that showed the results of acute temporary pacing studies had no correlation with outcome. Thus, there remains a discrepancy between perceived symptomatic benefit and modest objective improvement. Also, optimal outcome was achieved only with continued pharmacologic treatment.

Pacing in hypertrophic obstructive cardiomyopathy: A randomized crossover study	Kappenberger, L, Linde, C, Daubert, C, McKenna, W, Meisel, E, Sadouf, N, Chojnowska, L, Guize, L, Gras, D, Jeanrenaud, X, Ryden, L, and PIC Study Group. European Heart Journal.1997;18:1249-1256 (34)	To determine the intermediate term outcome of DDD pacing in patients with HCM.	Randomized multicenter single blind crossover study. Patients then randomized to 12 wks of activated pacing or inactivated pacing in a single blind crossover study.	83 patients (mean age 53 :25-87 y)	Patients with obstructive HCM and severe symptoms refractory to drug therapy. The patients all had acute hemodynamic response to pacing.	Symptoms, exercise duration, and gradient	NYHA class improved from 2.4 to 1.4 for dyspnea and 1.0 to 0.4 for angina ($p<0.007$). Quality of life showed improvement. After 12 wks of pacing, the gradient fell from 59 +/- 36 to 30 +/- 25 mmHg with active pacing. Exercise tolerance improved by 21%, but only in those patients who at baseline had a severe limitation of <10 min at Bruce protocol.	This trial showed clinical and hemodynamic benefit for patients with hypertrophic obstructive cardiomyopathy and LVOT obstruction. This multicenter trial included only patients who had an acute hemodynamic response >30% reduction in gradient in the catheterization laboratory. There was no overall change in exercise time when looking at all patients. Although 70% improved, the degree of improvement was not related to acute hemodynamic results.
Dual-chamber pacing for hypertrophic cardiomyopathy: A randomized, double-blind, crossover trial	Nishimura, R, Trusty, J, Hayes, D, Ilstrup, D, Larson, K, Hayes, S, Allison, T, Tajik, A. JACC.1997;29:435-441 (35)	To determine the intermediate term outcome of DDD pacing in patients with HCM	Randomized double-blind crossover study. Patients randomized for 3 mo each of DDD pacing and back-up AAI pacing.	21 patients (Mean age 58; 35-74 y).	Single center trial of selected patients with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO_2.	Six mo of follow-up, LVOT gradient had decreased from 76 +/- 61 to 55 +/- 38 mmHg after DDD pacing and 83 +/- 59 mmHg after AAI pacing. Quality of life and exercise duration were significantly improved from the baseline state compared to the DDR, but not significantly different between the DDD arm and the back-up arm. 63% of patients had symptomatic improvement during the DDD arm, but 42% had symptomatic improvement during the AAI arm. Peak oxygen consumption did not differ significantly. Symptoms did not change in 31% and 5% experienced deterioration of symptoms.	This trial showed that dual-chamber pacing may relieve symptoms and decrease gradient in patients with HCM, but there are some patients in whose symptoms do not change and become even worse. Symptomatic improvement may occur without hemodynamic benefit suggesting the role of a placebo effect.
Significant improvement of quality of life following atrioventricular synchronous pacing in patients with hypertrophic obstructive cardiomyopathy. Data from 1 year of follow-up	Gadler, F, Linde, C, Daubert, C, McKenna, W, Meisel, E, Aliot, E, Chojnowska, L, Guize, L, Gras, D, Jeanrenaud, X, Kappenberger, L. European Heart Journal.1999.20:1044-1050 (36)	To determine the outcome of pacing on quality of life during 1 y follow-up.	Cohort trial - implant DDD pacemaker in all patients	83 patients (mean age 53, 32-87 y).	Patients with obstructive HCM and severe symptoms refractory to drug therapy.	NYHA class and Karolinska quality of life.	At the end of 1 y, no patient had hemodynamic deterioration. NYHA Class I (36 patients follow-up vs. 0 patients initial); NYHA class II (31 patients follow-up vs. 37 patients initial); NYHA class III (8 patients follow-up vs./ 45 patients initial). 76 of the patients preferred pacing and 4 patients preferred AAI mode.	This study showed that atrioventricular synchronous pacing had a beneficial effect on most domains of quality of life at 1 y follow-up.

Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY)	Maron, B, Nishimura, R, McKenna, W, Rakowski, H, Josephson, M, Kieval, S. Circulation 1999:99:2927-2933 (37)	To determine the intermediate term outcome of DDD pacing in patients with HCM.	Randomized double-blind crossover study. DDD pacing implants in all patients, randomized then to a DDD mode and pacing back-up AAI mode in a double-blind crossover study design, followed by an uncontrolled 6-mo pacing trial.	48 patients (age 53 +/- 17, 22-83 y).	Patients with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO_2.	DDD versus AAI mode comparison at 6 mo indicated no significant change in exercise capacity, quality of life, or NYHA class. During a 12-mo follow-up of 6 further mo of continuous pacing, there was a significant increase in functional class and quality of life, but no change in peak oxygen consumption. The gradient was reduced from 82 +/- 32 mmHg to 48 +/- 32 mmHg. There was no change in gradient in 43%. Only 12% had a clinical response (improvement in NYHA class, quality of life, treadmill time), and these were all patients >65 years old.	This trial showed perceived symptomatic improvement was most consistent with a substantial placebo effect during the randomization process. Longer uncontrolled pacing periods had subjective benefit, but did not have objective improvement in cardiovascular performance and there was only modest reduction in outflow tract gradient.
Dual chamber pacing for patients with hypertrophic obstructive cardiomyopathy: A clinical perspective in 2000.	Erwin, J, Nishimura, R, Lloyd, M, Tajik, A. Mayo Clin Proc.2000;75:173-180. (38)	To determine the long-term outcome of patients with HCM.	Cohort trial (single center) DDD pacemakers implanted in all patients	28 patients (56 +/- 16 y)	Patients with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms and LVOT gradient.	At a follow-up of 24 +/- 14 mo (max 50 mo), 47% of patients improved but 53% of patients did not improve in terms of symptomatic response. LVOT gradient decreased from 95 +/- 40 to 62 +/- 47 mmHg.	This is a much lower "success" rate with long-term follow-up of patients who underwent dual-chamber pacing, with less than half of the patients having symptomatic improvement. There was no difference in the gradient response between those patients who improved versus those who did not improve. The residual gradient was still > 60 mmHg, which is severe obstruction.
Long-term follow-up of patients with obstructive hypertrophic cardiomyopathy treated with dual-chamber pacing.	Megevand, A, Ingles, J, Richmond, D, Semsarian, C. Am J Cardiol.2005;95:991-993. (39)	To determine the long-term outcome of DDD pacing in patients with HCM.	Single center cohort trial. DDD pacemaker implanted in all patients.	18 patients (mean age 47 y)	Patients with obstructive HCM and severe symptoms refractory to drug therapy. Only patients who had an initial acute hemodynamic benefit	Outflow tract gradient and NYHA class	At the end of a follow-up of 49 +/- 33 mo, the gradient of 82 +/- 35 dropped to 32 +/- 23. There was a beneficial result in NYHA class from 2.4 to 1.8.	This study reports the long-term outcome of a cohort of patients who had a dual-chamber pacemaker implanted who had a beneficial acute hemodynamic study. There was a significant reduction in symptoms as well as sustained decrease in LVOT obstruction at a follow-up of over four years.

HCM indicates hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Hear Association; and VO_2, oxygen consumption.

Data Supplement 4. Sudden Cardiac Death Risk Factor Table

Study Name	Author (Citation)	Aim of study	Study Design	Study Size	Patient Population	Endpoints	Results							Comments
								FHSCD	MLVWT	NSVT	SYNCOPE	ABPR	LVOTO	Multiple RF	
Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy.	Sadoul N, Prasad K, Elliott PM, et al. Circulation 1997;96:2987–91 (40)	Assess prognostic significance of blood pressure response to exercise in HCM patients	Single center prospective data collection of consecutive patients	161 patients	HCM patients ≤40 y of age	Sudden Death	Univariate					OR: 3.0, p<0.005			
							Multivariate								
Sudden death in hypertrophic cardiomyopathy: Identification of high risk patients.	Elliott PM, Poloniecki J, Dickie S, et al. Journal of the American College of Cardiology 2000;36:2212-2218 (41)	Identify HCM patients at high risk for SCD	Single center prospective data collection of consecutive patients	368 patients	HCM patients. Exclusions: prior SCD event, current amiodarone use, incomplete risk assessment <40 y of age	Sudden Death	Univariate	p=0.15	**OR: 4.1, p=0.001**	p=0.21	p=0.13	**OR: 2.4, p=0.04**		**2 or more RF: OR: 5.6, p=0.0001**	
							Multivariate	**Combined with syncope (OR: 5.3, p=0.002)**	**OR: 2.9, p=0.03**	p=0.18	**Combined with family history (OR: 5.3, p=0.002)**	p=0.22			
Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study.	Maron BJ, Savage DD, Wolfson JK, et al. Am J Cardiol 1981;48:252–7 (42)	Assess prognostic significance of 24 hour ambulatory ECG monitoring in HCM patients	Single center prospective data collection of consecutive patients	84 patients	HCM patients. Exclusions: myectomy patients	Sudden Death	Univariate			p=0.02					
							Multivariate								
Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia.	Spirito P, Rapezzi C, Autore C, et al. Circulation. 1994;90:2743–7. (43)	Assess prognostic significance of NSVT in asymptomatic or mildly symptomatic	3 center retrospective study	151 patients	HCM Patients. Exclusions: prior syncope, NYHA class >2; any cardioactive medications	Sudden Death	Univariate			p=0.24					

		HCM patients					Multivariate									
Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy assessment in an unselected non-referral based patient population.	Cecchi F, Olivotto L, Montereggi A, Squillatini G, Dolara A, Maron BJ. Heart 1998;79:331-336 (44)	Evaluate antiarrhythmic therapy in HCM patients	Single center registry	167 patients	HCM Patients. Exclusions: amiodarone use and/or absence of 24 h ambulatory ECG	Cardiac and Sudden Death	Univariate			NS						Only 1 sudden death in entire study population
							Multivariate									
Predictors of sudden cardiac death in hypertrophic cardiomyopathy.	Maki S, Ikeda H, Muro A, et al. Am J Cardiol. 1998;82:774–8 (45)	Identify HCM patients at high risk for SCD	Single center data collection.	309 patients	HCM patients, consecutive	Sudden Death	Univariate	**p=0.03**	p=0.33	p=0.41	p=0.07	**p=0.0002**	**p=0.0009**			
							Multivariate									
Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy	Spirito P. Bellone P. Harris KM. Bernabo P. Bruzzi P. Maron BJ. New England Journal of Medicine. 2000 342(24):1778-85 (46)	Assess the relation between LVH and survival in HCM patients	2 centers retrospective data collection	480 patients	HCM Patients; excluded patients with prior cardiac arrest and/or no follow up	Sudden Death	Univariate	p=0.23					**p=0.0006**			
							Multivariate		**OR: 1.76 per 5 mm increase, p=0.003**				p=0.76			
Relation between severity of left ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy.	Elliott PM, Gimeno B, Jr, Mahon NG, Poloniecki JD, McKenna WJ. Lancet 2001;357:420-424 (47)	Assess prognostic significance of LVH in relation to other SCD risk factors	Single center data collection.	630 patients	HCM patients, consecutive	Sudden Death or ICD discharge	Univariate		**OR: 1.31 per 5 mm increase, p=0.03**					**OR: 2.1, p=0.0001**		

							Multivariate		OR: 1.26 per 5 mm increase, p=0.06					**OR: 2.0, p=0.0001**	
Maximum left ventricular thickness and risk of sudden death in patients with hypertrophic cardiomyopathy.	Olivotto I. Gistri R. Petrone P. Pedemonte E. Vargiu D. Cecchi F. Journal of the American College of Cardiology. 41(2):315-21, 2003 (48)	Assess relationship between LVH and outcome in HCM patients	Single center data collection.	237 patients	HCM patients, consecutive	Sudden Death or ICD discharge	Univariate		p=0.27						
							Multivariate								
Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy.	Elliott PM, Gimeno JR, Tome MT, et al. Eur Heart J. 2006;27:1933– 41 (49)	Assess influence of symptoms and LVOTO on risk for SCD in HCM patients	Single center data collection.	917 patients	HCM patients, consecutive	Sudden Death or ICD discharge	Univariate							**OR: 1.8-2.0, p<0.001**	
							Multivariate	**OR: 1.9, p=0.04**	p=0.2	**OR: 3.8, p<0.0001**	**OR: 2.3, p=0.01**	p=0.3	**OR: 1.01 per mmHg, p=0.002**		**OR: 3.8 if LVOTO >90 mmHg, p=0.005**
Syncope and risk of sudden death in hypertrophic cardiomyopathy.	Spirito P, Autore C, Rapezzi C, et al. Circulation. 2009; 119: 1703–1710 (50)	Assess clinical implications of syncope in HCM patients	Multicenter data collection	1511 patients	HCM patients, consecutive	Sudden Death or ICD discharge	Univariate				p=0.08				
							Multivariate	p=0.12	p=0.06		p=0.29;		p=0.29		**For unexplained syncope <6 mo prior to evaluation, OR: 4.9, p=0.006**

ABPR indicates abnormal blood pressure response; ECG, electrocardiogram; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MLVWT, maximum left ventricular wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; RF, risk factor; and SCD, sudden cardiac death.

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