

- surements determined at cardiac catheterization. *Am J Cardiol* 1991;67:1007-12.
14. Carabello BA. Evaluation and management of patients with aortic stenosis. *Circulation* 2002;105:1746-50.
 15. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;343:611-7.
 16. Dehmer GJ, Firth BG, Hillis LD, et al. Alterations in left ventricular volumes and ejection fraction at rest and during exercise in patients with aortic regurgitation. *Am J Cardiol* 1981;48:17-27.
 17. Nistri S, Sorbo MD, Marin M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart* 1999;82:19-22.
 18. Svensson LG, Kim KH, Lytle BW, Cosgrove DM. Relationship of aortic cross-sectional area to height ratio and the risk of aortic dissection in patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg* 2003;126:892-3.
 19. Rahimtoola SH. Choice of prosthetic heart valve for adult patients. *J Am Coll Cardiol* 2003;41:893-904.
 20. Borer JS, Herrold EM, Hochreiter C, et al. Natural history of left ventricular performance at rest and during exercise after aortic valve replacement for aortic regurgitation. *Circulation* 1991;84:III133-9.

Appendix 1

The authors of this report declared they have no relationships with industry pertinent to this topic.

Task Force 4: HCM and Other Cardiomyopathies, Mitral Valve Prolapse, Myocarditis, and Marfan Syndrome

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HYPERTROPHIC CARDIOMYOPATHY

General considerations. Hypertrophic cardiomyopathy (HCM) is a relatively common form of genetic heart disease (0.2%; 1:500 in the general population) (1), and the most common cause of sudden unexpected cardiac death in young people, including competitive athletes (2). Sudden death may occur at any age, but is most common in individuals 30 years of age or less. At present, 12 mutant genes (most encoding sarcomeric proteins) and over 400 specific mutations in these genes have been implicated in the pathogenesis of clinically diagnosed HCM (3).

The disease is characterized by heterogeneous presentation and natural history in which the most consistent diagnostic feature demonstrated by echocardiography is otherwise unexplained and usually asymmetric hypertrophy associated with a non-dilated left ventricle (LV) (3-5). Clinical diagnosis of HCM is made by recognition of the disease phenotype with LV hypertrophy (3,4). In this regard, a maximal LV end-diastolic wall thickness of 15 mm or more (or on occasion, 13 or 14 mm) is the absolute dimension generally accepted for the clinical diagnosis of HCM in an adult athlete (in children, 2 or more standard deviations from the mean relative to body surface are; z-score of 2 or more); however, any LV wall thickness (including normal) is theoretically compatible with the presence of a mutant HCM gene (3,4). Of note, individuals of virtually any age (but usually less than 14 years old) harboring a HCM-causing mutant gene may not manifest LV hypertrophy (3,4).

In a disease such as HCM, extrapolation of risk level

from non-athletes to highly trained competitive athletes is tenuous. This relates to the unstable electrophysiologic substrate and propensity for potentially lethal ventricular tachyarrhythmias in HCM, interacting with the physiologic stresses inherent in athletic training and competition (i.e., alterations in blood volume, hydration, and electrolytes). Furthermore, no single clinical, morphologic, or electrophysiologic factor has emerged as the reliable predictor of risk in HCM (3,4). Therefore, because the panel could not precisely stratify sudden death risk specifically for all athletes with HCM, the present recommendations for sports eligibility remain conservative and homogeneous for those athletes within the diverse HCM clinical spectrum.

Given the inability to precisely stratify risk on clinical grounds in individual young patients with HCM, a broad recommendation to exclude such individuals from competitive sports will, by definition, deny participation to some unnecessarily. However, given the frequency with which HCM is associated with sudden death in young athletes (2), and recent data showing that athletic activity per se is associated with higher risk in those with underlying cardiovascular abnormalities (6), the present recommendations are viewed as prudent. That is, the goal is to encompass all preventable sudden deaths in young persons with HCM, while acknowledging that other athletes who may not be destined for sudden death will also be subjected to the same recommendations.

Preclinical diagnosis. With the availability of preclinical genetic diagnosis, a relatively small number of youthful family members have been identified as affected by a HCM-causing mutant gene solely on the basis of laboratory

DNA analysis, and in the absence of typical morphologic (phenotypic) features of the disease (3,4). As family genetic screening for HCM becomes more widespread, clinicians may be increasingly faced with the dilemma of making recommendations regarding sports participation for subjects who have only preclinical evidence of HCM (i.e., genotype positive-phenotype negative). Nonetheless, it is likely that most such individuals are destined to ultimately develop the HCM phenotype with the attendant possibility of a potentially unstable electrophysiologic milieu. Moreover, the HCM phenotype (i.e., LV hypertrophy) may develop over the course of several years (3,4) after initial evaluation, when competitive sports participation could still be an ongoing and important lifestyle issue.

Based on these considerations, prudent recommendations for athletes with preclinical HCM would include, on a 12- to 18-month basis, in addition to serial two-dimensional echocardiography: 12-lead ECG and ambulatory Holter electrocardiogram (ECG), and less frequently cardiac magnetic resonance (CMR) imaging and exercise stress testing to a level similar to that expected in the sport under consideration (for evaluation of exercise tolerance, blood pressure, and ventricular tachyarrhythmias). If all of these parameters continue to be normal, then based on the level of present knowledge, restriction from competitive athletic activities is not recommended. Such systematic follow-up of this subgroup is strongly recommended, particularly if there is a family history of HCM and sudden cardiac death.

Relevant to these considerations are the prior observations that abnormalities on 12-lead ECG and preload-independent measures of diastolic dysfunction with tissue Doppler ultrasonography may precede the appearance of LV hypertrophy, providing clues to impeding development of wall thickening (7-9). Athletes with abnormal 12-lead ECG and absence of LV hypertrophy on two-dimensional echocardiogram (particularly if relatives in HCM families) should be afforded a high index of suspicion for HCM and undergo CMR imaging to determine whether areas of segmental hypertrophy undetected by echocardiography are present in regions of the LV chamber such as anterolateral free wall or apex (7). However, 12-lead ECG abnormalities in family members without LV hypertrophy (particularly if relatively minor or nonspecific) should not per se be regarded as evidence of HCM.

Recommendations:

1. Athletes with a probable or unequivocal clinical diagnosis of HCM should be excluded from most competitive sports, with the possible exception of those of low intensity (class IA). This recommendation is independent of age, gender, and phenotypic appearance, and does not differ for those athletes with or without symptoms, LV outflow obstruction, or prior treatment with drugs or major interventions with surgery, alcohol septal ablation, pacemaker, or implantable defibrillator.

2. Although the clinical significance and natural history of genotype positive-phenotype negative individuals remains unresolved, no compelling data are available at present with which to preclude these patients from competitive sports, particularly in the absence of cardiac symptoms or a family history of sudden death.

Given the effectiveness of implantable cardioverter-defibrillators (ICDs) in preventing sudden death in HCM (10), clinicians will increasingly be faced with decisions regarding athletic participation for HCM patients with ICDs. Although effective for sudden death prevention in observational studies (10), the unique physiologic milieu associated with competitive athletic activities, including intravascular volume and electrolyte disturbances, neurohormonal activity, and the potential for myocardial ischemia make the absolute reliability of ICDs in such settings unpredictable. Furthermore, there is a possibility for device malfunction and the risk for traumatic injury to the athlete-patient (or other competitors) should the ICD discharge either appropriately or inappropriately. Thus, the placement of an ICD in an HCM patient does not change the competitive sports recommendations for this disease (as previously noted), namely, that restriction from participation in contact and most non-contact sports is advisable (11); such individuals may engage only in low-intensity competitive sports (class IA).

The presence of a free-standing automated external defibrillator (AED) at sporting events should not be considered either absolute protection against sudden death, a prospectively designed treatment strategy for known cardiovascular disease, nor a justification for participation in competitive sports in athletes with previously diagnosed HCM. Athletes with HCM using drugs such as anabolic steroids or energy stimulant drinks may in fact increase their risk of arrhythmias, although definitive data are lacking.

MITRAL VALVE PROLAPSE (MVP)

Mitral valve prolapse (i.e., myxomatous degeneration) is of particular importance in the evaluation of athletes, given its relatively high prevalence in the general population (estimated, 2% to 3%) (12-14). The condition is defined by echocardiography as systolic displacement of one or both mitral leaflets into the left atrium beyond the plane of the mitral annulus in the parasternal long-axis view (13). These patients may be identified by auscultation with a mid-systolic click and/or murmur of mitral regurgitation. Additionally, MVP is characterized by a mostly favorable prognosis and low event rate (12-15). In general, the greatest risks for unfavorable clinical sequelae—which include severe progressive mitral regurgitation requiring valve surgery, infective endocarditis, embolic events, atrial and ventricular tachyarrhythmias, and sudden death appear to be associated with substantial structural abnormality of the mitral valve (i.e., “classic” MVP) with diffuse leaflet thickening, elonga-

tion, and redundancy, and in some cases ruptured chordae tendineae (12–15).

Sudden cardiac death due to isolated MVP is rare among young patients, particularly in relation to exercise and/or in trained athletes (12–16). Such events are probably not more frequent than in the general population and occur predominantly in patients older than 50 years with severe mitral regurgitation and/or systolic dysfunction (15).

Some individuals with MVP appear to be part of a connective tissue phenotypic spectrum with tall, thin habitus, thoracic cage deformity, and joint hypermobility (i.e., MASS phenotype), for which there is a risk, albeit low, for progression to aortic dilatation or sudden death (17).

Recommendations:

1. **Athletes with MVP—but without any of the following features—can engage in all competitive sports:**
 - a. **prior syncope, judged probably to be arrhythmogenic in origin**
 - b. **sustained or repetitive and nonsustained supraventricular tachycardia or frequent and/or complex ventricular tachyarrhythmias on ambulatory Holter monitoring**
 - c. **severe mitral regurgitation assessed with color-flow imaging**
 - d. **LV systolic dysfunction (ejection fraction less than 50%)**
 - e. **prior embolic event**
 - f. **family history of MVP-related sudden death**
2. **Athletes with MVP and any of the aforementioned disease features can participate in low-intensity competitive sports only (class IA).**

Recommendations related to hemodynamic burden secondary to moderate–severe mitral regurgitation (as assessed by physical examination and two-dimensional echocardiogram and Doppler study) in athletes with MVP appear in Task Force 3.

MYOCARDITIS

Myocarditis is an inflammatory disease of myocardium and a cause of sudden death in young athletes (2,18–24). It is usually of infectious etiology due to a variety of viral agents, most commonly enterovirus (e.g., Coxsackie virus), adenovirus, or parvovirus in young people, but also by drugs and toxic agents such as cocaine (22–25). Myocarditis evolves through active, healing, and healed pathologic stages—characterized progressively by inflammatory cell infiltrates leading to interstitial edema and focal myocyte necrosis and replacement fibrosis (20)—which potentially create an electrically unstable substrate for development of ventricular tachyarrhythmias (2,18,24). In some instances, viral myocarditis can culminate in dilated cardiomyopathy with LV systolic dysfunction, presumably as a consequence of viral-mediated immunologic damage to the myocardium or cytoskeletal disruption (22–25).

Myocarditis can be diagnosed by established histopathologic, histochemical, or molecular criteria (20,23–25), but is challenging to identify clinically. Suspicion may be raised by chest pain, exertional dyspnea, fatigue, syncope, palpitations, ventricular tachyarrhythmias and conduction abnormalities or by acute congestive heart failure associated with LV dilatation and/or segmental systolic dysfunction, cardiogenic shock, or ST-T changes on ECG (22,24).

When clinical judgment suggests the presence of myocarditis, an endomyocardial biopsy may clarify an otherwise ambiguous clinical profile. Because of patchy distribution of inflammatory cells, biopsies are often insensitive and frequently yield false-negative histologic results (20,22,24). However, the diagnostic yield of histology can be enhanced by molecular analysis with PCR amplification of the viral genome (23,25).

Recommendations:

1. **Athletes with probable or definite evidence of myocarditis should be withdrawn from all competitive sports and undergo a prudent convalescent period of about six months following the onset of clinical manifestations.**
2. **Athletes may return to training and competition after this period of time if:**
 - a. **LV function, wall motion, and cardiac dimensions return to normal (based on echocardiographic and/or radionuclide studies at rest and with exercise)**
 - b. **clinically relevant arrhythmias such as frequent and/or complex repetitive forms of ventricular or supraventricular ectopic activity are absent on ambulatory Holter monitoring and graded exercise testing**
 - c. **serum markers of inflammation and heart failure have normalized**
 - d. **the 12-lead ECG has normalized. Persistence of relatively minor ECG alterations such as some ST-T changes are not, per se, the basis for restriction from competition.**

MARFAN SYNDROME

Marfan syndrome (and related disorders), caused by more than 400 individual mutations in the gene encoding fibrillin-1 (FBN1), is an autosomal dominant disorder of connective tissue with estimated prevalence of 1:5,000 to 1:10,000 in the general population (26–29). It is characterized clinically by a diverse constellation of abnormalities variable in severity and involving primarily the ocular, skeletal, and cardiovascular organ systems (28–30). Diagnosis is made according to the Gent nosology if major criteria are present in two organ systems and a third is involved, or when there is a family history of Marfan syndrome (28,29). Skeletal abnormalities include arm span-to-height ratio greater than 1.05, tall stature, arachnodactyly, dolichostenomelia (long, thin limbs), hyperextensibility

and ligamentous laxity, scoliosis, and chest wall deformity (pectus excavatum or carinatum), in addition to ectopia lentis (lens dislocation).

Cardiovascular manifestations that impact on natural history are: 1) progressive dilatation of the aortic root or descending aorta, which predisposes to dissection and rupture (30-33); and 2) MVP with associated mitral regurgitation or LV systolic dysfunction, which may occasionally predispose to ventricular tachyarrhythmias and sudden death (33). The risk for aortic rupture is usually linked to marked enlargement of the aorta (transverse dimension greater than 50 mm), although dissection can occur with a normal (or near-normal) aortic root dimension (30-36) (A. DePaepe, personal communication, April 12, 2004). Weightlifting has been specifically associated with aortic dissection in athletes with cystic medial necrosis (with or without systemic hypertension or use of anabolic steroids) (35,36). The incidence of aortic dissection appears to have decreased with earlier prophylactic surgical aortic root reconstruction and beta-blocker therapy (30,32,34).

Ascending aortic root dilatation (and dissection) has also been associated with congenital bicuspid aortic valve disproportionate to that attributable to abnormal valvular function (37-41), as well as familial aortic aneurysm and dissection, independent of Marfan syndrome (41-43).

Recommendations:

1. **Athletes with Marfan syndrome can participate in low and moderate static/low dynamic competitive sports (classes IA and IIA) if they do not have one or more of the following:**
 - a. **aortic root dilatation (i.e., transverse dimension 40 mm or greater in adults, or more than 2 standard deviations from the mean for body surface area in children and adolescents; z-score of 2 or more)**
 - b. **moderate-to-severe mitral regurgitation**
 - c. **family history of dissection or sudden death in a Marfan relative**

It is recommended, however, that these athletes have an echocardiographic measurement of aortic root dimension repeated every six months, for close surveillance of aortic enlargement.
2. **Athletes with unequivocal aortic root dilatation (transverse dimension 40 mm or greater in adults or greater than 2 standard deviations beyond the mean for body surface area in children and adolescents; z-score of 2 or more) (41,43), prior surgical aortic root reconstruction, chronic dissection of aorta or other artery, moderate-to-severe mitral regurgitation, or family history of dissection or sudden death can participate only in low-intensity competitive sports (class IA).**
3. **Athletes with Marfan syndrome, familial aortic aneurysm or dissection, or congenital bicuspid aortic valve with any degree of ascending aortic enlargement (as defined in 1 and 2 above) also should not participate**

in sports that involve the potential for bodily collision.

4. **Recommendations related to aortic regurgitation are the same as those in Task Force 3.**

These recommendations are offered independent of whether beta-blockers are administered to mitigate aortic root enlargement.

EHLERS-DANLOS SYNDROME

The vascular form of Ehlers-Danlos syndrome carries a substantial risk of rupture of the aorta and its major branches (28). This is a rare autosomal dominant disorder, caused by a defect in type III collagen, encoded by the COL3A1 gene. Patients have variable joint hypermobility, susceptibility to bruising, difficult wound healing, and often prematurely aged appearance.

Recommendation:

1. **Individuals with the vascular form of Ehlers-Danlos syndrome should not engage in any competitive athletic activity.**

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Cited as a major cause of sudden death in young people and athletes (44-46), particularly in the northeastern (Veneto) region of Italy (45) but seemingly less common in the U.S (2,18), ARVC is characterized by a broad phenotypic spectrum and characteristically by loss of myocytes in the right ventricular myocardium with fatty or fibro-fatty replacement resulting in segmental or diffuse wall thinning. It is frequently associated with myocarditis (44,45,47). Clinical diagnosis is challenging, but relies largely on familial occurrence, ventricular tachyarrhythmias (particularly ventricular tachycardia of right ventricular origin elicited by exercise), T-wave inversion in precordial leads V₁ through V₃ and epsilon waves on ECG, or right ventricular dilatation and/or segmental wall motion abnormalities, aneurysm formation, and fatty deposition in the right ventricular wall identified with echocardiography, multi-slice computed tomography, or cardiac magnetic resonance imaging.

Recommendation:

1. **Athletes with probable or definite diagnosis of ARVC should be excluded from most competitive sports, with the possible exception of those of low intensity (class IA).**

OTHER MYOCARDIAL DISEASES

A number of other uncommon diseases of the myocardium deserve consideration as potential causes of sudden death in athletes. These include dilated cardiomyopathy (due to a variety of etiologies including genetic); primary non-hypertrophied restrictive cardiomyopathy, systemic infiltra-

tive diseases with secondary cardiac involvement such as sarcoidosis, and also isolated non-compaction of LV myocardium with or without systolic dysfunction (48,49). Few data are presently available regarding the relative risks of athletic training and competition in athletes with the aforementioned myocardial diseases.

Recommendation:

1. **Until more information is available in this regard, it is most prudent to exclude athletes with these diseases from most competitive sports, with the possible exception of those of low intensity (class IA) in selected cases.**

PERICARDITIS

Recommendation:

1. **Athletes with pericarditis, regardless of etiology, should not participate in competitive sports during the acute phase. Such athletes can return to full activity when there is no longer evidence of active disease, including effusion by echocardiography, and when serum markers of inflammation have normalized. For pericarditis associated with evidence of myocardial involvement, eligibility recommendations should also be based on the course of myocarditis. Chronic pericardial disease that results in constriction disqualifies one from all competitive sports.**

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TASK FORCE 4 REFERENCES

1. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4,111 subjects in the CARDIA study: Coronary Artery Risk Development In (young) Adults. *Circulation* 1995;92:785-9.
2. Maron BJ. Sudden death in young athletes. *N Engl J Med* 2003;349:1064-75.
3. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687-713.
4. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287:1308-20.
5. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. *Circulation* 1995; 92:1680-92.
6. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2003;42:1959-63.
7. Rosenzweig A, Watkins H, Hwang DS, et al. Preclinical diagnosis of familial hypertrophic cardiomyopathy by genetic analysis of blood lymphocytes. *N Engl J Med* 1991;325:1753-60.
8. Panza JA, Maron BJ. Relation of electrocardiographic abnormalities to evolving left ventricular hypertrophy in hypertrophic cardiomyopathy. *Am J Cardiol* 1989;63:1258-65.
9. Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation* 2002;105:2992-7.
10. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000;342: 365-73.
11. Maron BJ, Mitten MJ, Quandt EF, Zipes DP. Competitive athletes with cardiovascular disease—the case of Nicholas Knapp. *N Engl J Med* 1998;339:1632-5.
12. Nishimura RA, McGoon MD, Shub C, Miller FA Jr., Ilstrup DM, Tajik AJ. Echocardiographically documented mitral-valve prolapse: long-term follow-up of 237 patients. *N Engl J Med* 1985;313:1305-9.
13. Marks AR, Choong CY, Sanfilippo AJ, Ferre M, Weyman AE. Identification of high-risk and low-risk subgroups of patients with mitral-valve prolapse. *N Engl J Med* 1989;320:1031-6.
14. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1-7.
15. Avierinos JF, Gersh BJ, Melton LJ III, et al. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation* 2002;106:1355-61.
16. Corrado D, Basso C, Nava A, Rossi L, Thiene G. Sudden death in young people with apparently isolated mitral valve prolapse. *G Ital Cardiol* 1997;27:1097-105.
17. Glesby MJ, Pyeritz RE. Association of mitral valve prolapse and systemic abnormalities of connective tissue: a phenotypic continuum. *JAMA* 1989;262:523-8.
18. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes: clinical, demographic, and pathological profiles. *JAMA* 1996;276:199-204.
19. Phillips M, Robinowitz M, Higgins JR, Boran KJ, Reed T, Virmani R. Sudden cardiac death in Air Force recruits: a 20-year review. *JAMA* 1986;256:2696-9.
20. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3-14.
21. Karjalainen J, Heikkila J. Incidence of three presentations of acute myocarditis in young men in military service: a 20-year experience. *Eur Heart J* 1999;20:1120-5.
22. Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol* 1991;18:1617-26.
23. Bowles NE, Ni J, Kearney DL, et al. Detection of viruses in myocardial tissues by polymerase chain reaction. Evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol* 2003;42:466-72.
24. Towbin JA. Myocarditis. In: Finberg L, Kleinman R, editors. *Saunders Manual of Pediatric Practice*. Philadelphia, PA: WB Saunders, 2002:660-3.
25. Martin AB, Webber S, Fricker FJ, et al. Acute myocarditis: rapid diagnosis by PCR in children. *Circulation* 1994;90:330-9.
26. Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-9.
27. Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrilopathies. *J Med Genet* 2000;37:9-25.
28. Pyeritz RE. Marfan syndrome and other disorders of fibrillin. In: Rimoin DL, Conner JM, Pyeritz RE, Korf B, editors. *Principles and Practice of Medical Genetics*. 4th edition. Edinburgh: Churchill Livingstone, 2002:3977-4020.
29. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-26.
30. Januzzi JL, Isselbacher EM, Fattori R, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004;43:665-9.
31. Marsalese DL, Moodie DS, Vacante M, et al. Marfan's syndrome: natural history and long-term follow-up of cardiovascular involvement. *J Am Coll Cardiol* 1989;14:422-8.
32. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335-41.
33. Yetman AT, Bornemeier RA, McCrindle BW. Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death? *J Am Coll Cardiol* 2003;41:329-32.
34. Gott VL, Greene PS, Alejo DE, et al. Replacement of the aortic root in patients with Marfan's syndrome. *N Engl J Med* 1999;340:1307-13.

35. de Virgilio C, Nelson RJ, Milliken J, et al. Ascending aortic dissection in weight lifters with cystic medial degeneration. *Ann Thorac Surg* 1990;49:638-42.
36. Elefteriades JA, Hatzaras I, Tranquilli MA, et al. Weight lifting and rupture of silent aortic aneurysms. *JAMA* 2003;290:2803.
37. Ferencik M, Pape LA. Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. *Am J Cardiol* 2003;92:43-6.
38. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol* 1992;19:283-8.
39. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol* 1991;17:712-6.
40. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart* 1999;82:19-22.
41. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol* 2004;44:138-43.
42. Lewin MB, McBride KL, Pignatelli R, et al. Echocardiographic evaluation of asymptomatic parental and sibling cardiovascular anomalies associated with congenital left ventricular outflow tract lesions. *Pediatrics* 2004;114:691-96.
43. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol* 1989;64:507-12.
44. Tabib A, Loire R, Chalabreysse L, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation* 2003;108:3000-5.
45. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol* 1997;30:1512-20.
46. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2003;108:3084-91.
47. Bowles NE, Ni J, Marcus F, Towbin JA. The detection of cardiotropic viruses in the myocardium of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2002;39:892-5.
48. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol* 2000;36:493-500.
49. Pignatelli RH, McMahon CJ, Dreyer WJ, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003;108:2672-8.

Appendix 1. Author Relationships With Industry and Others

Name	Consultant	Research Grant	Scientific Advisory Board	Stock Holder	Expert Witness Testimony
Dr. Michael J. Ackerman	<ul style="list-style-type: none"> • CV Therapeutics • Genaisance Pharmaceuticals • Medtronic • Pfizer 	None	<ul style="list-style-type: none"> • Genaisance Pharmaceuticals 	<ul style="list-style-type: none"> • Genaisance Pharmaceuticals 	None
Dr. Barry J. Maron	None	<ul style="list-style-type: none"> • Medtronic 	None	None	<ul style="list-style-type: none"> • 1996, Defense, Northwestern vs. Knapp
Dr. Rick A. Nishimura	None	None	None	None	None
Dr. Reed E. Pyeritz	<ul style="list-style-type: none"> • Genzyme 	<ul style="list-style-type: none"> • Genzyme 	None	None	None
Dr. Jeffrey A. Towbin	None	None	None	None	<ul style="list-style-type: none"> • 2005, Defense, Myocarditis, sudden death in child • 2004, Defense, Myocarditis, sudden death in child • 2004, Defense, Myocarditis, sudden death in child • 2002, Defense, Myocarditis, sudden death in child • 2000, Defense, Myocarditis, sudden death in child • 1996, Plaintiff, Myocarditis, sudden death in professional athlete • 1995, Plaintiff, Myocarditis, sudden death in professional athlete
Dr. James E. Udelson	None	None	None	None	None