Editorial

Prophylactic Implantable Defibrillators for Hypertrophic Cardiomyopathy
Disarray in the Era of Precision Medicine

Andrew Grace, MB, PhD

Discussions with individuals and families affected by hypertrophic cardiomyopathy (HCM) concerning prophylactic implantable defibrillators (ICDs) will on occasion offer some new challenges. In a bold attempt to provide categorical answers, the European Society of Cardiology have incorporated a mathematical approach to risk prediction into their 2014 guidelines[1] that includes some risk factors (RFs) that are not broadly agreed and without any prior independent testing.[2] Furthermore, 2 groups have now examined how the guidance would have performed in their patients and arrived at essentially polar opposite conclusions on utility.[3,4]

Article see p 829

HCM is common with a broad clinical expression and overall an annual sudden cardiac death (SCD) risk that is <1%.[5,6] It is the exemplar monogenic cardiac disorder and study of the underlying genetics has enhanced understanding of disease pathophysiology opening up candidate therapeutic approaches.[7] More complete follow-up along with multidisciplinary considerations of the range of treatment options has allowed better timing of surgical/nonsurgical interventions.[1,6] Such progress has had a significant impact on improving patient outcomes, but there is the critical issue that we remain only modestly capable of identifying accurately the small subset that will benefit from an ICD.[1,3,4,8]

Why risk prediction remains so difficult has been extensively considered.[1,5] Despite large patient cohorts, it is the phenotypic diversity of HCM, the low SCD event rates, the long recruitment periods, evolving assessment methods and corresponding incomplete data that have all confounded clear answers. The only option for the provision of protection is the ICD and prospective, randomized comparisons have not been possible.[9] Accordingly, guidance has relied on cumulative clinical observation.[5,6,8] What is agreed is that individual RFs that have been associated with risk have low positive predictive

power, in the range of 10% to 20%,[5] and even with aggregate RF assessment sensitivity and specificity in regard to the prediction of SCD remains poor.[5] Family history is undoubtedly relevant, but epigenetic and other acquired influences have substantially greater impact on risk so that genetic studies have few roles in SCD risk assessment in the propositus.[1]

Possible RFs have been the subject of long-standing dispute on both their definition and relative importance.[1,4,10] These include syncope,[10] ventricular wall thickness, exercise-associated blood pressure responses, nonsustained ventricular tachycardia, and left ventricular outflow tract (LVOT) obstruction.[11] One point that is striking is that neither the nature nor the number of RFs predicts ICD discharge.[9,12] Furthermore, factors previously not considered risk markers, eg, fractional shortening, have been associated with appropriate shocks thereby again questioning individual RF validity.[12] Simply stacking up RFs has low predictive power strongly supported by an observational, retrospective, cohort study of 1606 patients in whom 5 RFs were assessed in their capacity to predict risk.[13] Although risk was seen to increase with multiple RFs, the *C*-statistic obtained from the receiver operating characteristic curve (in the range 0.61 to 0.64 at 5 years) indicated limited capacity to resolve risk.[13] These data essentially recapitulate prior evidence provided from a prospective evaluation of the same RFs.[14] The results taken together provide substantial support for the view that softer but nonetheless effective contributions such as physician experience are crucial to making the right decisions.[1,4,5]

The HCM Risk-SCD algorithm has been presented with an aim "to develop and validate a new SCD prediction model that provides individualized risk estimates"[2] and is the basis of the European Society of Cardiology 2014 risk guidance.[1] The algorithm is based on a Cox proportional hazards model internally validated with boot strapping. The data populating the model was obtained from a retrospective, multicenter, longitudinal cohort study involving 3675 consecutively presenting patients. The model was developed across 5 sites (2082 patients) with validation at a further participating center (1593 patients). Seven continuous or binary RFs (age, maximal LV wall thickness, left atrial [LA] size, max. LVOT gradient, family history of SCD, nonsustained ventricular tachycardia, and unexplained syncope) derived from the literature and each independently associated with SCD in at least one multivariable survival analysis were then assessed in respect of the occurrence of SCD or appropriate ICD shocks. These events occurred in ≈5% of patients over a median follow-up of 5.7 years. Patients were then banded into one of 3 groups based on 5-year risks of SCD. If the 5-year risk was calculated at <4%, an ICD would not be recommended; if in the range 4% to 6%, it would be contingent; and if >6%, an

ICD would be recommended. The *C*-statistic reported using this modified approach was 0.70. RFs can now be inputted into an online calculator (doc2do.com/hcm/webHCM.html) and a recommendation obtained as to whether to recommend or seek out ICD implantation.[1]

The predictor variables included in the HCM Risk-SCD algorithm that have probably attracted most comment are LA enlargement and LVOT obstruction. At first pass, LA enlargement is not the most intuitively obvious potential predictor of the risk of SCD. The incorporation in the algorithm has been justified by a single observation in which LA enlargement conferred a relative risk of 1.03 (confidence interval, 1.00–1.06; *P*<0.04).[10] LA enlargement has been used, rather than the presence of atrial fibrillation, as we are told: "LA enlargement predisposes to atrial fibrillation and contained less missing data."[2] A further problem is that the association between atrial fibrillation and SCD in HCM has never been robust and in a recent study of 3673 patients, although atrial fibrillation enhanced overall risk, there was no significant influence on the risk of SCD.[15] The problems raised by the inclusion of LVOT obstruction mainly relate to frequency of occurrence, variability, and modest impact.[4]

The performance of the HCM Risk-SCD algorithm has now been assessed in an observational cohort design conducted in twin tertiary referral centers.[3] A total of 706 HCM patients who had been under consideration for a prophylactic ICD have been included, and the end points of SCD-equivalent event (SCD, appropriate ICD discharge) was observed in 5.9% of patients at follow-up. Interestingly, basal LVOT gradient was >30 mm in 53% patients, and >30% of patients underwent interventions that could have had a significant impact on key inputs into the algorithm (LVOT gradient, LA size). Of course, we already know that relief of LVOT obstruction with myectomy is associated with subsequent low rates of SCD.[16] The research provides similar results to those in the first description of HCM Risk-SCD[2] with an improved *C*-statistic (0.69) when compared with derivations based on the 2003[17] (*C*-statistic, 0.55) and 2011[5] guidance (*C*-statistic, 0.60). Using this approach still required the implantation of 17 ICDs to save one life at the end of 5 years.

To directly test the algorithm, a US group has also retrospectively examined the clinical prediction capabilities of HCM Risk-SCD in 1629 consecutive patients followed up for a median of 6.4 years of whom 460 received ICDs.[4] Forty-six patients went on to receive appropriate ICD interventions, but 27 (59%) of this group had low HCM Risk-SCD scores that would have precluded an ICD recommendation. In addition, only 16 of the total of 81 (20%) who had an SCD-equivalent event had a high HCM Risk-SCD score along with a definite ICD recommendation. This group also tested the algorithm in a series of simulations providing examples of patients with large single RFs (who would not receive an ICD according to HCM Risk-SCD) and situations such as a combination of relative youth, LVOT obstruction, and increased LA size (who would not currently receive an ICD but in whom with uncritical application of HCM Risk-SCD would now get an ICD). The main conclusion was that application of HCM Risk-SCD might reduce the number of inappropriate ICDs but was thoroughly insensitive to the accurate identification of high-risk patients.[4]

In view of these various continuing issues, it is likely that most of us will (for now) steer clear of an algorithmic approach that might obscure useful raw data.[1,2] Some patients will undoubtedly access the HCM Risk-SCD algorithm, input their own data, and raise possibly challenging questions that will need to be addressed. To minimize such occurrences, a single, inclusive community effort in guideline formulation based on international cooperation should again be our aim.[17] Most experienced physicians will continue to take a careful history probing difficult aspects (family history, syncope), review all the data in multidisciplinary discussion, and reach a measured conclusion to take back to the well-informed patient. Patients without manifest RFs will be reassured in the knowledge that their risk is low and not too far away from the general population mean.[5] The question of risk will be revisited at future visits in the light of their further test results and accumulating research findings.[5] In those in whom an ICD is thought likely to provide net benefit, the simplest device possible for that patient should be used to minimize adverse risks.[12] This may be a single ventricular lead, single-coil transvenous unit but consideration should be made of the subcutaneous ICD, especially in young patients who will be especially prone to the issues emerging from both acute and progressive lead failure.[9,12,18,19]

The variable performance of the HCM risk-SCD algorithm again highlights the need for new methods to identify those at risk of ventricular fibrillation.[20] It is universally agreed that the source of risk is myocardial, and that the presence of myofibrillar disarray is a key determinant yet no current assessment method addresses this aspect directly.[5,6,14] The use of late gadolinium enhancement as a possible means of risk stratification is of great interest, but it is unlikely to be sensitive to the presence of disarray.[21] Gadolinium is taken up into expanded extracellular spaces and detects large areas of scar tissue during washout but smaller patches of collagen, interstitial fibrosis, and disarray may not be detected.[21,22] Late gadolinium enhancement is, however, relevant to HCM-related heart failure outcomes,[22] and although the relationship to SCD outcomes is not yet secure and probably again modest, it associates with potential surrogates of SCD (hypertrophy, nonsustained ventricular tachycardia).[22,23] The American College of Cardiology /American Heart Association guidelines support a potential role of late gadolinium enhancement in decision making[5] although whether the absence of late gadolinium enhancement predict those at low risk remains a point of much discussion.[8,23,24] The National Institutes of Health–funded HCMR (Novel Predictors of Outcome in HCM) study plans to recruit 2750 subjects with 5-year follow-up to address the question of the best use of advanced imaging in risk stratification and is due for completion in 2018.[25]

Developments of cardiac MRI technology, eg, T1 mapping,[26] will no doubt usefully input into phenotypic categorization. It would, however, appear that the architectural pattern not the density of fibrosis had the most impact on the electrophysiology of human cardiomyopathic hearts when studied ex vivo.[27,28] So while diffuse, short-strand fibrosis had marginal effects on conduction delay, patchy fibrosis with long fibrotic strands substantially delayed conduction[27] and such patterns are more likely to facilitate wavebreak and fibrillation.[29] The

direction of wavefront activation is also of relevance to the occurrence of nonuniform anisotropic conduction with effects being the most prominent with activation perpendicular to fiber direction.[27] Clearly, some elements of this complex structural/functional milieu are going to be more amenable to noninvasive imaging than others.

Invasive electrophysiological assessment of patients with HCM is not usually recommended having fallen out of favor after disappointing, contentious responses to conventional ventricular stimulation.[1,5] Nonetheless, evidence of regional voltage variation, increased latency, and delayed conduction has been consistently observed.[30,31] In addition, the feasibility of invasive assessment of electrograms with the aim of addressing the functional significance of myofibrillar disarray without arrhythmia induction has been reported.[14] The capacity of such approaches to enhance risk prediction was strongly supported in a prospective study of 179 patients followed up over 4 years. This investigation demonstrated that the electrophysiological approach predicted outcome with a high PPV (*C*-statistic, 0.88) although further validation is required.[14]

The ICD provides an effective means of protecting HCM patients from SCD but we must precisely target high-risk subcategories of the disease to gain most benefit.[32] To make further significant progress, we require a focus on deep phenotyping (imaging/electrophysiology) directed to the heart muscle to address the prognostic consequences of myofibrillar disarray. In the interim, as Spiegelhalter has pointed out, we should be cautious in the use of large data sets as "precision will delude us if selection bias and overinterpretation of associations as causation are not properly taken into account."[33]

Sources of Funding

Disclosures

References

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.
2. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020. doi: 10.1093/eurheartj/eht439.
3. Vriesendorp PA, Schinkel AFL, Liebregts M, Theuns DAMJ, van Cleemput J, ten Cate FJ, Willems R, Michels M. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2015;8:829–835. doi: 10.1161/CIRCEP.114.002553.
4. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the european society of cardiology sudden death risk model for hypertrophic cardiomyopathy [published online ahead of print June 4, 2015]. *Amer J Cardiol*. 2015. doi: 10.1016/j.amjcard.2015.05.047. http://www.ajconline.org/article/S0002-9149(15)01431-9/abstract.
5. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e783–e831. doi: 10.1161/CIR.0b013e318223e2bd.
6. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol*. 2015;65:1915–1928. doi: 10.1016/j.jacc.2015.02.061.
7. Ashrafian H, McKenna WJ, Watkins H. Disease pathways and novel therapeutic targets in hypertrophic cardiomyopathy. *Circ Res*. 2011;109:86–96. doi: 10.1161/CIRCRESAHA.111.242974.
8. McKenna WJ, Nagueh SF. Cardiac magnetic resonance imaging and sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130:455–457. doi: 10.1161/CIRCULATIONAHA.114.010977.
9. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA III, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298:405–412. doi: 10.1001/jama.298.4.405.
10. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barillà CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation*. 2009;119:1703–1710. doi: 10.1161/CIRCULATIONAHA.108.798314.
11. Elliott P, Gimeno J, Tomé M, McKenna W. Left ventricular outflow tract obstruction and sudden death in hypertrophic cardiomyopathy. *Eur Heart J*. 2006;27:3073; author reply 3073–3073; author reply 3074. doi: 10.1093/eurheartj/ehl383.
12. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-Shaikh S, Rahman SM, Arnous S, Jones S, McKenna W, Elliott P. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart*. 2012;98:116–125. doi: 10.1136/hrt.2010.217182.
13. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ, Elliott PM. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Heart*. 2013;99:534–541. doi: 10.1136/heartjnl-2012-303271.
14. Saumarez RC, Pytkowski M, Sterlinski M, Bourke JP, Clague JR, Cobbe SM, Connelly DT, Griffith MJ, McKeown PP, McLeod K, Morgan JM, Sadoul N, Chojnowska L, Huang CL, Grace AA. Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy. *Eur Heart J*. 2008;29:1653–1661. doi: 10.1093/eurheartj/ehn111.
15. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc*. 2014;3:e001002. doi: 10.1161/JAHA.114.001002.
16. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, Schaff HV, Tajik AJ, Gersh BJ. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J*. 2007;28:2583–2588. doi: 10.1093/eurheartj/ehm117.
17. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED; Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. 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;42:1687–1713.

18. Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE Study and EFFORTLESS Registry. *J Am Coll Cardiol*. 2015;65:1605–1615. doi: 10.1016/j.jacc.2015.02.047.

19. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation*. 2007;115:2474–2480. doi: 10.1161/CIRCULATIONAHA.106.663807.

20. Grace AA, Roden DM. Systems biology and cardiac arrhythmias. *Lancet*. 2012;380:1498–1508. doi: 10.1016/S0140-6736(12)61462-7.

21. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, Petrou M, Pennell DJ. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;43:2260–2264. doi: 10.1016/j.jacc.2004.03.035.

22. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart*. 2014;100:1851–1858. doi: 10.1136/heartjnl-2013-305471.

23. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130:484–495. doi: 10.1161/CIRCULATIONAHA.113.007094.

24. Maron MS, Maron BJ. Clinical impact of contemporary cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy. *Circulation*. 2015;132:292-298. doi: 10.1161/CIRCULATIONAHA.114.014283.

25. US National Institutes of Health. HCMR: Novel Markers of Prognosis in Hypertrophic Cardiomyopathy. https://clinicaltrials.gov/ct2/show/NCT01915615. Accessed July 25, 2015.

26. Puntmann VO, Voigt T, Chen Z, Mayr M, Karim R, Rhode K, Pastor A, Carr-White G, Razavi R, Schaeffter T, Nagel E. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. *JACC Cardiovasc Imaging*. 2013;6:475–484. doi: 10.1016/j.jcmg.2012.08.019.

27. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, Hauer RN, Kirkels H, Janse MJ, de Bakker JM. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. *Circulation*. 2001;104:3069–3075.

28. Glukhov AV, Fedorov VV, Kalish PW, Ravikumar VK, Lou Q, Janks D, Schuessler RB, Moazami N, Efimov IR. Conduction remodeling in human end-stage nonischemic left ventricular cardiomyopathy. *Circulation*. 2012;125:1835–1847. doi: 10.1161/CIRCULATIONAHA.111.047274.

29. Engelman ZJ, Trew ML, Smaill BH. Structural heterogeneity alone is a sufficient substrate for dynamic instability and altered restitution. *Circ Arrhythm Electrophysiol*. 2010;3:195–203. doi: 10.1161/CIRCEP.109.890459.

30. Schumacher B, Gietzen FH, Neuser H, Schümmelfeder J, Schneider M, Kerber S, Schimpf R, Wolpert C, Borggrefe M. Electrophysiological characteristics of septal hypertrophy in patients with hypertrophic obstructive cardiomyopathy and moderate to severe symptoms. *Circulation*. 2005;112:2096–2101. doi: 10.1161/CIRCULATIONAHA.104.515643.

31. Sakamoto N, Kawamura Y, Sato N, Nimura A, Matsuki M, Yamauchi A, Kanno T, Tanabe Y, Takeuchi T, Natori S, Saijo Y, Aburano T, Hasebe N. Late gadolinium enhancement on cardiac magnetic resonance represents the depolarizing and repolarizing electrically damaged foci causing malignant ventricular arrhythmia in hypertrophic cardiomyopathy. *Heart Rhythm*. 2015;12:1276–1284. doi: 10.1016/j.hrthm.2015.02.004.

32. Ashley EA. The precision medicine initiative: a new national effort. *JAMA*. 2015;313:2119–2120. doi: 10.1001/jama.2015.3595.

33. Spiegelhalter DJ. Statistics. The future lies in uncertainty. *Science*. 2014;345:264–265. doi: 10.1126/science.1251122.

Prophylactic Implantable Defibrillators for Hypertrophic Cardiomyopathy: Disarray in the Era of Precision Medicine
Andrew Grace

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circep.ahajournals.org/content/8/4/763