There is a subset of patients with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction who have severely limiting symptoms despite optimal medical therapy.\(^1\) Septal reduction therapy, consisting of a surgical procedure (septal myectomy) or a catheter-based therapy (alcohol septal ablation), has been used to treat this subset of patients. A successful procedure will abolish the left ventricular outflow tract obstruction and result in dramatic relief of symptoms, allowing these patients with severe debilitation to return to a near-normal lifestyle.

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For most of these medication-refractory patients, septal myectomy has been considered the “gold standard” for treatment.\(^2\) Since its first introduction in the 1960s, there has been a continued decrease in operative mortality and an increase in overall success rate primarily due to improvements in operative technique and myocardial protection. In the hands of experienced surgeons, the mortality for an isolated septal myectomy is \(<1\%\), and \(>90\%\) of patients are able to achieve sustained clinical improvement. Modern data also support that survival is equivalent to the general population after successful septal myectomy.\(^3\) Alcohol septal ablation emerged in the mid-1990s as a percutaneous alternative to septal myectomy.\(^4\) There was a high initial enthusiasm for alcohol septal ablation because early results demonstrated that relief of obstruction and improvement of symptoms could be accomplished with a low procedural complication rate.\(^5\) Although surgical myectomy was limited to a few tertiary referral centers, many catheterization laboratories across the world began to perform alcohol septal ablation.

However, after the introduction of alcohol septal ablation, case reports emerged describing the occurrence of potentially lethal arrhythmias on follow-up.\(^6,7\) MRI scanning with gadolinium enhancement demonstrated a large “scar” in the myocardium at the site of the alcohol ablation, signifying a localized myocardial infarction.\(^8\) There was concern that creation of a scar in patients with hypertrophic cardiomyopathy who were already at increased risk for ventricular arrhythmias may result in a long-term detrimental outcome.\(^9\) Nonetheless, according Leonardi et al.,\(^10\) “despite thousands of ablations, a possible increased risk of sudden death after alcohol septal ablation has not been substantiated nor refuted.”

The Leonardi et al.\(^10\) study is a metaanalysis that compares both overall mortality and sudden cardiac death mortality in patients undergoing septal myectomy versus patients undergoing septal ablation. The authors performed a sophisticated comparative data analyses using a random effects model and regression analysis. From 795 published studies regarding the outcome of these procedures, they selected 27 comprising \(>4000\) patients who had septal reduction therapy. When the authors adjusted for available baseline characteristics, alcohol septal ablation had a better outcome than septal myectomy in terms of both overall mortality and sudden cardiac death. The metaanalysis also showed an equivalent improvement in New York Heart Association class following the 2 procedures.

Patients and physicians would prefer, of course, the less-invasive percutaneous procedure to open heart surgery if clinical outcomes were similar after both procedures and if there was a decreased risk of sudden death after alcohol septal ablation.\(^5\) However, despite these data and other grouped analyses, surgical myectomy still remains the “gold standard” for septal reduction therapy in the minds of experienced clinicians with an expertise in treating patients with hypertrophic cardiomyopathy.\(^1,9,11,12\) Thus, it is of critical importance that the cardiology community be made aware of several major caveats outlined here that may not be evident from reading the article by Leonardi et al.\(^10\) but are well-known to those who have an understanding of the disease.

1. Sudden death in patients with hypertrophic cardiomyopathy is unpredictable, with a particularly long-term risk implicit in these relatively young patients.\(^13\) In registry studies of implanted automatic defibrillators in patients with hypertrophic cardiomyopathy, patients have been shown to remain event free for decades after implantation and then to suddenly develop a life-threatening ventricular arrhythmia.\(^14\) Thus, long-term follow-up (over decades) is essential to determine whether there is a detrimental effect of any procedure in terms of increasing the risk of sudden death in patients with hypertrophic cardiomyopathy. Although many myectomy studies have follow-up exceeding 10 years, approximately half of the studies of alcohol septal ablation in this metaanalysis have a follow-up of \(<1\)
1. The technique of alcohol septal ablation is evolving and varies from institution to institution. The varied techniques may contribute to differences in the risk of sudden death after the procedure. Some centers perform an alcohol septal ablation by selecting multiple septal branches and using 2 to 5 mL of alcohol. Others perform the procedure by selecting smaller branches of a septal perforator artery and infusing <1.5 mL of alcohol. The larger amounts of alcohol produce larger areas of infarction, and although this may result in a better hemodynamic outcome, the larger dose may result in a higher incidence of future ventricular arrhythmias.

2. There is concern regarding the completeness of the follow-up data in this metaanalysis. For instance, in just 2 of the studies of alcohol septal ablation, 56 patients were lost to follow-up. Because there were only 26 documented sudden cardiac deaths in all combined studies, the relatively large number of patients lost to follow-up may have a significant effect on the validity of the results. The lack of critically important information contained in this metaanalysis is evident in the reported follow-up of patients who received an automatic defibrillator. In the patients undergoing alcohol septal ablation, >100 had a defibrillator implanted, with only 1 reporting appropriate shock; this is in marked contrast to previous studies of patients with defibrillators after alcohol septal ablation, including a multicenter registry that demonstrated a rate of appropriate defibrillator discharge of 5% to 10% per year.14,15

3. There is a wide spectrum of sudden death risk in patients with hypertrophic cardiomyopathy. Although hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes, population studies of patients with this condition have shown mortality rates of <1% per year; a mortality rate comparable with that of an age- and sex-matched control population.16 Thus, emphasis has been placed on identifying risk factors for sudden death, including family history of hypertrophic cardiomyopathy and sudden death, a personal history of unexplained syncope, massive hypertrophy, nonsustained ventricular tachycardia, and abnormal exercise blood pressure response.1,17 If a comparison is to be made regarding the risk of sudden death after 2 different interventions in patients with hypertrophic cardiomyopathy, it would be important to understand the baseline risk of sudden death in each group. These data are not available in this metaanalysis.

4. The technique of alcohol septal ablation is evolving and varies from institution to institution. The varied techniques may contribute to differences in the risk of sudden death after the procedure. Some centers perform an alcohol septal ablation by selecting multiple septal branches and using 2 to 5 mL of alcohol. Others perform the procedure by selecting smaller branches of a septal perforator artery and infusing <1.5 mL of alcohol. The larger amounts of alcohol produce larger areas of infarction, and although this may result in a better hemodynamic outcome, the larger dose may result in a higher incidence of future ventricular arrhythmias.

5. The results of the metaanalysis suggest similar outcomes between alcohol septal ablation and septal myectomy in terms of symptom relief assessed by changes in New York Heart Association class, yet previous studies consistently document higher procedural hemodynamic success rates with septal myectomy (>90%) than with septal ablation (≈75%), and there is a greater degree of symptomatic improvement in patients undergoing septal myectomy versus septal ablation.18,19 Although direct surgical resection of the region of hypertrophied myocardium that causes obstruction can be uniformly performed, the success of alcohol septal ablation depends on the anatomic relationship of a septal perforator to the myocardium. Because of the highly variable anatomy of the septal perforator arteries, the interventional cardiologist may not always be able to target the area of systolic anterior motion-septal contact during an alcohol septal ablation.8 The assumption that the hemodynamic and clinical benefit of both alcohol septal ablation and septal myectomy are equivalent would be misleading.

The article by Leonardi et al10 is a sophisticated statistical exercise; however, it is important to assure that critical decisions regarding patient care be based on all available data. Although there is no definitive evidence of an increased risk of sudden death after septal ablation versus septal myectomy, we caution against using a metaanalysis to support the converse. We appreciate the power of a metaanalysis in gathering data from large numbers of patients in the absence of randomized controlled studies. However, the calculated, very low 0.4% per year rate of sudden death after septal ablation in the present metaanalysis is of concern. Comprehensive data from hypertrophic cardiomyopathy centers with meticulous methodology and complete follow-up cannot be ignored. An annual event rate (ventricular tachycardia/ventricular fibrillation, cardiac arrest, or implantable defibrillator firing) of 4.9% per year in patients with implantable defibrillators after septal ablation was reported from a well-respected hypertrophic cardiomyopathy institution,15 an incidence similar to other studies.14 Two thirds of these patients had 0 risk factors for sudden death, placing them in a group that would be expected to have an sudden cardiac death rate of 0.4% to 0.9%.20 The event rate among the patients with ≥1 risk factor was even higher at 13.4% per year. Although the incomplete data in the metaanalysis does not include most risk factors, a history of syncope was reported in a one third of patients who underwent ablation, indicating that the population studied was not uniformly of low risk. These discrepant data between the results of the metaanalysis and established literature must be taken into consideration.

Hypertrophic cardiomyopathy is a complex diverse disease process, and important decisions regarding invasive therapies should be made based on all available data as well as on clinical experience and expertise. A well-performed metaanalysis is always a welcome addition to the literature. However, it is difficult to reconcile the conclusion that alcohol septal ablation has a lower overall mortality and sudden death rate versus septal myectomy in the face of existing data, especially given the caveats discussed earlier. We would propose that clinicians caring for patients with hypertrophic cardiomyopathy consider the following when deciding on appropriate therapy for symptomatic patients with hypertrophic cardiomyopathy and obstruction.

- Septal reduction therapy has been shown to improve symptoms, but no data show that it prolongs life or prevents sudden death. Thus, the indication for septal reduction therapy is severe, limiting symptoms unresponsive to optimal medical management. Candidates for septal reduction therapy must have a suitable anatomy accompa-
nied by a severe resting and a provocative dynamic left ventricular outflow obstruction associated with systolic anterior motion of the mitral valve.

- Both septal myectomy and alcohol septal ablation are effective therapies to relieve obstruction and improve symptoms in properly selected patients with obstructive hypertrophic cardiomyopathy. Septal myectomy results in a more complete relief of obstruction, with a higher percentage of patients free of severe symptoms during follow-up, particularly in those aged <65 years. Although the overall risk of each procedure highly depends on the experience of the operator and patient selection, there is a higher incidence of heart block requiring implantation of a permanent pacemaker after alcohol septal ablation.

- There are still no definitive data to indicate that alcohol septal ablation either increases or decreases the incidence of ventricular arrhythmias or sudden death. Long-term complete follow-up that takes into consideration the wide spectrum of underlying baseline risk and diversity of procedural technique will be required to answer this question. It must be recognized that events (ventricular tachycardia/ventricular fibrillation, sudden death, and implantable defibrillator firing) do occur after ablation.14-15

- Irrespective of whether septal myectomy or alcohol septal ablation is chosen, these procedures should only be performed by experienced operators in conjunction with a multidisciplinary team that can properly evaluate, advise, and treat the patient. A full comprehensive understanding of the literature and clinical experience is necessary for both physicians and patients to make a well-informed decision regarding the indication for and type of septal reduction therapy.

**Disclosures**

None.

**References**


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Septal Reduction Therapy for Obstructive Hypertrophic Cardiomyopathy and Sudden Death: What Statistics Cannot Tell You
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