

KEY ARTICLES

Key Articles and Guidelines in the Management of Arrhythmias, 2004–2010

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The volume of medical literature in the management of cardiovascular diseases has continued to grow exponentially. It is important for clinical practitioners to keep informed in order to provide optimal patient care. We compiled a list of pertinent clinical trials, as well as well-written, up-to-date review articles and important treatment guidelines, that focus on the management of cardiac arrhythmias. This list is an update to a previous list published in *Pharmacotherapy* in 2004. This article should be useful not only to practitioners and trainees in cardiovascular pharmacotherapy, but to other clinicians as well.

Key Words: atrial fibrillation, ventricular arrhythmias, treatment guidelines, key articles.

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Since 2004, the Cardiology Practice & Research Network of the American College of Clinical Pharmacy has undertaken the initiative to compile lists of key references in different cardiovascular (CV) disease areas (e.g. hypertension, hyperlipidemia, acute coronary syndromes, heart failure [HF] and arrhythmias). In the last two years, it was determined that these

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lists need to be updated as new and pertinent medical literature continue to become available and that all the previously published list were extremely well received by clinicians and trainees.

This list in the updated series includes some of the most pertinent literature in the area of cardiac arrhythmia management. After performing a thorough literature search, the authors consented that the references included here are among the most important ones published since 2004 (when the previous list was published). This list contains the most important literature that serves as the basis of some of our standards of practice today.

ATRIAL FIBRILLATION – PHARMACOLOGIC MANAGEMENT

Rate versus Rhythm Control

Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation (RATE II). *N Engl J Med* 2010;362:1363–73.

The RATE II trial was designed to compare a lenient rate control strategy to a typical strict rate

control strategy in atrial fibrillation (AF). Patients (n=614) with permanent AF were randomized to a lenient (resting heart rate < 110 beats per minute) or a strict (resting heart rate < 80 beats per minute or exercise heart rate < 110 beats per minute) rate control group. The primary end point of the study was a composite of CV death, HF hospitalization, stroke or embolism, bleeding or life threatening arrhythmia. This study was a non-inferiority study with the definition of non-inferiority being met if the upper bound of the 90% confidence interval (CI) for the absolute difference in the primary end point between groups was less than 10%. Patient follow-up was 2–3 years. The primary end point was achieved in 12.9% of the lenient control group and 14.9% of the strict control group (absolute difference [90% CI = -2.0% [-7.6–3.5%]). Therefore the definition of non-inferiority was met. The authors concluded that a lenient rate control strategy was non-inferior to a strict rate control strategy. This is the first study to evaluate the impact of strict versus lenient heart rate control; however, some limitations should be mentioned. First, the end point used in this study was the same as that used in RATE I, which was a rate control vs. rhythm control study. While a composite end point that includes stroke and bleeding may be relevant for a rate vs. rhythm study, this end point may not be as relevant for a study that investigates rate control of different intensities. Additionally, while the average heart rates achieved by the two study groups differed statistically, clinical significance of this difference could be debated (lenient: 85±14 beats per minute, strict: 76±14 beats per minute). This study is important because it may suggest that it is appropriate to use a lenient heart rate control approach if a strict approach is not feasible.

Shelton RJ, Clark AL, Goode K, et al. A randomized, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). *Heart* 2009; 95:924–30.

This is a follow-up study to the original CAFÉ study, which compared a rate versus rhythm control strategy in AF. The CAFÉ II evaluated the impact of a rate versus rhythm control strategy on quality of life (QOL) and exercise tolerance in a patient population with persistent AF and symptomatic systolic HF. Patients (n=61) were randomized to a rate control (resting heart rate < 80 beats per minute or exercise heart rate

of < 110 beats per minute) or rhythm control (oral amiodarone ± electrical cardioversion) strategy. At 1 year, QOL was assessed with the Medical Outcomes Study Short Form-36 (SF-36) and exercise tolerance was assessed by a 6-minute walk test (primary outcomes). Left ventricular (LV) function was also assessed by echocardiography at 1 year. Patients in the rhythm control group had an improved QOL at 1 year, particularly those who remained in sinus rhythm (SR). Exercise tolerance was similar between the two groups; however, when only those achieving the rate control target in the rate group were compared to only those in SR in the rhythm group, exercise tolerance was improved with rhythm control. Patients in the rhythm control group also experienced a greater improvement in LV function at 1 year. This study adds to the literature because it suggests that while there may not be a mortality benefit associated with a rhythm control strategy in patients with HF, there may be QOL advantages. Therefore, the use of a rhythm control strategy may be warranted in selected patients whose QOL is particularly impacted by their cardiac disease.

Nabauer M, Gerth A, Limbourg T, et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace* 2009;11:423–34.

This paper describes data from a national AF registry in Germany. Patients were entered into the registry through both hospital and clinic encounters. A total of 9582 patients were entered into the registry over a 2-year timeframe. Patients with paroxysmal (30.2%), persistent (19.5%) and permanent (32.8%) AF were included in the registry. The registry provides a snapshot of current practice related to AF in Germany. Extensive demographic and clinical characteristic data are presented for the different types of AF. The registry suggests that β-blockers and digoxin are more commonly used than calcium channel blockers (CCBs) for rate control. This paper also suggests that rhythm control is being used in about 50% of patients with AF, regardless of whether symptoms are present or not. The most commonly used antiarrhythmic drugs (AADs) in a rhythm control strategy were flecainide and amiodarone. This registry raises questions about current practice surrounding AF in the United States. It is unclear whether practice in Germany would be similar or different. Interestingly, the use of a

rhythm control strategy appeared to still be common among asymptomatic patients, despite current guidelines and literature.

Dankner R, Shahar A, Novikov I, Agmon U, Ziv A, Hod H. Treatment of stable atrial fibrillation in the emergency department: a population-based comparison of electrical direct-current versus pharmacological cardioversion or conservative management. *Cardiology* 2009;112:270–8.

This study was designed to identify the optimal strategy for managing AF in the emergency department. This was a retrospective observational study that included 374 patients. Patients had to be in persistent AF and hemodynamically stable to be included in the study. The cohort was divided into 3 groups, those treated with electrical cardioversion, pharmacologic cardioversion or a “watch and wait” approach. Propensity score weighting was used to limit the influence of confounders on study outcomes. Conversion rate was highest for those patients treated with electrical cardioversion (78.2%), as compared to the pharmacologic conversion (59.2%) and watch and wait (37.9%) groups ($p < 0.001$). Rate of discharge from the emergency department was also highest among those undergoing electrical cardioversion (52.9%, 47.9%, 32.1%, respectively). Rate of rehospitalization within 14 days was low in the overall population (3.4%), suggesting that complications among these patients with AF were uncommon after treatment in and discharge from the emergency department. Therefore, it may be possible for some patients with recurrence of AF to be discharged from the emergency department, instead of being treated as an inpatient.

McCabe JM, Johnson CJ, Marcus GM. Internal medicine physicians’ perceptions regarding rate versus rhythm control for atrial fibrillation. *Am J Cardiol* 2009;103:535–9.

This paper describes a survey of internal medicine physicians that assessed opinions regarding AF management. The survey response rate was approximately 19%, the mean age of participants was 49 ± 10 years, and most participants were in private practice (40%), academia (24%) or group practice (24%). Approximately 50% of respondents reported that they routinely manage patients with AF without a cardiologist. Sixty percent of survey respondents felt that rate control is the best strategy for managing AF, 22% felt rhythm

control is superior, and 18% felt the two strategies are equal. Top reasons for selecting a rate control strategy included “difficulty in maintaining SR” (48%) and “risk associated with AADs” (43%). Interestingly, 73% of respondents believed that stroke risk is less with a rhythm control strategy and 64% believe that mortality is less with a rhythm control strategy. This survey data is interesting because it highlights a conflict between existing literature/guidelines and the perceptions of internal medicine physicians.

GISSI AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med.* 2009;360:1606–17.

This study (also known as GISSI AF) was designed to test the hypothesis that an angiotensin receptor blocker (ARB) may impact rate of recurrence of AF. Prior to this study, several smaller prospective studies demonstrated a reduction in AF recurrence with an ARB in combination with amiodarone. In GISSI AF, patients ($n=1442$) with persistent AF were randomized to valsartan (target dose=320 mg daily) or placebo for a follow up period of 52 weeks. The primary end points of this study were time to first recurrence of AF and proportion of patients with multiple recurrences of AF in a one-year period. At 1 year, recurrence of AF was similar between groups (valsartan: 51.4%, placebo: 52.1%; $p=0.83$). More than one episode of AF recurrence occurred in 26.9% of patients in the valsartan group and 27.9% of patients in the placebo group ($p=0.34$). Median time to recurrence of AF was 295 days with valsartan and 271 days with placebo. The authors’ conclusion is that valsartan did not impact recurrence of AF. This study is important because it is the largest controlled clinical trial of an ARB for prevention of AF. However, a potential limitation of this study is that patients were only randomized to an ARB, rather than an ARB plus amiodarone, as was done in previous studies showing positive impact of ARBs on AF recurrence.

Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358:2667–77.

This study, also known as the AF-CHF study, was designed to determine whether a rate or rhythm control strategy was most appropriate for the patient with AF and systolic HF. Prior to publication of this study, there was considerable debate about the generalizability of major rate

versus rhythm studies (AFFIRM, RACE, etc) to a HF patient population. Patients (n=1376) with persistent AF and systolic HF were randomized to a rate control (target heart rate < 80 beats per minute) or rhythm control strategy. Follow-up was approximately 3 years. Rhythm control was achieved with serial electrical cardioversion and amiodarone was the drug of choice for maintaining SR. The primary outcome was CV death. There was no difference in the primary outcome between groups (HR 1.06; 95% CI 0.86–1.30; p=0.59). There was also no difference between groups in all-cause mortality, worsening of HF or stroke. There was a trend for a higher rate of hospitalization in the rhythm control group than in the rate control group (64% vs. 59%; p=0.06). The conclusion of this study was that clinical outcomes were similar between a rate and rhythm control strategy in a HF patient population. This study is important because it addressed the controversy surrounding whether or not a rate control strategy should be the preferred approach in patients with HF.

Allen Lapointe NM, Sun JL, Kaplan S, d'Almada P, Al-Khatib SM. Rhythm versus rate control in the contemporary management of atrial fibrillation in-hospital. *Am J Cardiol* 2008;101:1134–41.

This is an observational study that describes a snapshot of current practice related to AF based on data from 464 hospitals in the United States. The cohort was made up of 155,731 hospitalizations for AF. Rhythm control was the treatment strategy for 48% of the hospitalizations and rate control was used in 52%. Cardiologists were more likely to use a rhythm control strategy than non-cardiologists. The most commonly used AADs were amiodarone and sotalol. As age increased between 18 and 65 years, likelihood of a rhythm control strategy to be chosen increased. However, after the age of 65, likelihood of rhythm control use went down with increasing age. Calcium channel blockers were the most commonly used rate-controlling medication and digoxin was the least commonly used. A majority (57%) of hospitalizations where rate control was used involved the use of more than one rate-controlling agent. These data provide insight into current practice surrounding AF management in the United States. Interestingly, despite current guidelines that favor a rate control strategy for most patients, 50% of patients still receive a rhythm control strategy.

Hemels ME, Van Noord T, Crijs HJGM, et al.

Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *J Am Coll Cardiol* 2006;48:1001–9.

This was a randomized, open-label study which investigated the effect of routine versus acute electrical cardioversion and rate control with either verapamil or digoxin on the development of permanent AF. A routine electrical cardioversion strategy was defined as electrical cardioversion within 4–6 weeks of AF recurrence, while the acute strategy involved cardioversion within 24 hours of recurrence. Patients (n=144) with symptomatic persistent AF were first randomized to one of the rate control agents and then to acute or routine cardioversion. Patients who developed recurrence of AF could receive amiodarone or sotalol. No difference in development of permanent AF was noted between the acute and routine cardioversion groups at 18 months. There was also no difference in permanent AF between the digoxin and verapamil groups. However, the digoxin group underwent cardioversion more frequently (three vs. two episodes; p<0.001) over an 18-month period. Digoxin use was found to be an independent predictor of recurrence in multivariate regression analysis (hazard ratio [HR] 2.2; 95% CI 1.1–4.4; p=0.02). This study suggests that although choice of digoxin or verapamil has no impact on progression to permanent AF, there may be less need for cardioversion when verapamil is selected.

Ozaydin M, Varol E, Aslan SM, et al. Effect of atorvastatin on the recurrence rates of atrial fibrillation after electrical cardioversion. *Am J Cardiol* 2006;97:1490–3.

The hypothesis of this study was that the anti-inflammatory properties of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) could be useful in prevention of AF recurrence. In this prospective, randomized trial, 48 patients with persistent AF and a normal left ventricular ejection fraction (LVEF) were randomized to an atorvastatin (10 mg daily) or control group after electrical cardioversion. Study medication was administered 48 hours prior to cardioversion. Within 3 months of cardioversion, 12.5% of those randomized to atorvastatin and 45.8% in the control group experienced recurrence of AF (p=0.02). Atorvastatin was also an independent predictor of SR maintenance after adjustment for

confounding factors. In addition, C-reactive protein levels were reduced after cardioversion in the atorvastatin group (pre: 2.82 ± 1.46 , post: 2.56 ± 1.30 ; $p=0.02$), but did not change in the control group (pre: 2.87 ± 0.80 , post: 2.84 ± 0.80 ; $p=0.09$). This hypothesis-generating study is an important contribution to the growing body of literature supporting the role of medications that do not interact with ion-channels for the prevention of AF recurrence. It also highlights a potential role for anti-inflammatory therapies in the management of AF.

Olshansky B, Rosenfeld LE, Warner AL, et al, for the AFFIRM Investigators. The atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. *J Am Coll Cardiol* 2004;43:1201–8.

This was a post-hoc analysis of the AFFIRM trial, which focused on issues relating to rate control of AF. While the overall AFFIRM trial compared rate versus rhythm control of AF, this analysis examined the performance of digoxin, β -blockers and CCBs in the rate control arm of the study. Upon entry into AFFIRM, β -blockers (24%) were chosen as the rate controlling agent slightly more commonly than CCBs (17%), digoxin (16%), or the combination of either a β -blocker (14%) or CCBs (14%) with digoxin. Adequate rate control at rest and on exertion were qualitatively reported for each drug class. Adequate rate control was defined as an average heart rate ≤ 80 beats per minute and either a maximum heart rate on exertion of ≤ 110 beats per minute or average heart rate during 24-hour holter monitoring of ≤ 100 beats per minute. β -blocker therapy, either alone or in combination with digoxin, generally provided higher rates of acceptable rate control than other classes. Heart rate control on exertion was similar between digoxin (70%) and β -blocker therapy (72%), which is somewhat surprising given the lack of effect of digoxin on sympathetic stimulation. Approximately 40% of patients required a change in rate controlling agent over a 5-year period and over time; patients were more likely to be changed from digoxin or a CCB than a β -blocker. Rate control was well tolerated throughout the study follow-up. The overall conclusion of the analysis is that β -blockers are the most effective class of agents for rate control in AF; however, many patients will require changes in therapy for adequate rate control.

Opolski G, Torbicki A, Kosior DA, et al. Rate control vs. rhythm control in patients with

nonvalvular persistent atrial fibrillation. The results of the polish how to treat chronic atrial fibrillation (HOT CAFÉ) study. *Chest* 2004;126:476–86.

This study, also known as the HOT CAFÉ study, represents another addition to the literature evaluating the merits of rate versus rhythm control in the management of AF. Overall, this study is in agreement with other major trials in this area, suggesting that there is no major difference in patient outcomes when either a rate or rhythm control strategy is chosen. Patients ($n=205$) with persistent AF were randomized to rate control or rhythm control. The rhythm control group received multiple interventions in a stepwise fashion for maintaining SR. Patients in this group were first electrically cardioverted. If cardioversion was successful, disopyramide, propafenone, or sotalol was started. If initial cardioversion was unsuccessful, patients were started on amiodarone and cardioversion was attempted after adequate loading of the amiodarone. Recurrence of AF in patients on disopyramide, propafenone, or sotalol resulted in a change in therapy to amiodarone and repeat cardioversion. If recurrence occurred in patients while on amiodarone, patients were crossed over to the rate-control arm. Digoxin, β -blockers and CCBs were used in the rate-control arm and were titrated to a target ventricular rate of 70–90 beats per minute. All patients received adequate anticoagulation and the primary end point was all-cause mortality, thromboembolic complication or major hemorrhage. The composite end point did not differ between the rate and rhythm control group (odds ratio [OR] 1.98; 95% CI 0.28–22.3). The only differences between the two groups was improved exercise tolerance (maximal treadmill workload) in the rhythm control group and fewer hospitalizations with rate control (12% vs. 74%, $p<0.01$). This study adds to the body of literature suggesting that rate control could be considered as a first-line treatment strategy in many patients with AF.

Marshall DA, Levy AR, Vidaillet H, et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. *Ann Intern Med* 2004;141:653–61.

This was a pharmacoeconomic analysis of the landmark AFFIRM trial. The overall results of AFFIRM demonstrated no difference in survival between rate and rhythm control of AF and this study evaluated the incremental cost-

effectiveness ratio of the two strategies (dollars per life year gained) from the third-party payer perspective. All patients included in AFFIRM (n=4060) were included in this pharmacoeconomic analysis. Costs of procedures and hospitalization were derived from accepted sources and were specific to the year of completion of AFFIRM (2002). Drug cost was derived from the average wholesale price of the least expensive medication that was used in the two treatment arms. For each cost estimate, adequate sensitivity analyses were performed as well. Bootstrapping was also performed. Overall, resource utilization was lower in the rate-control group. In particular, hospitalization days and cardioversions were less with rate control. There was \$5077 savings per person with rate control and rate control was the dominant treatment strategy, as it was associated with longer survival and lower cost in bootstrapping analysis. Taken together with the main results of AFFIRM, this study suggests that a rate control method could be preferred for many patients with AF from both a clinical and economic standpoint.

Hagens VE, Ranchor AV, Sonderen EV, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the rate control versus electrical cardioversion (RACE) study. *J Am Coll Cardiol* 2004;43:241–7.

This study was designed to assess the influence of rate or rhythm control on QOL over 2-3 years. This was a substudy of the RACE study, which demonstrated a similar rate of CV events in patients with persistent AF randomized to rate or rhythm control. Quality of life assessments (Medical Outcomes Study SF-36) were completed in 352 study patients at baseline, 1 year and at the end of follow-up (2.3 years). This study demonstrated that patients with AF have lower QOL scores than healthy controls. The rate control group experienced improvement in QOL at one year, but by the end of the follow-up period, there was no difference between rate and rhythm control in QOL scores. Randomization to rate or rhythm control was not a significant predictor of improvements in QOL. Factors that did predict improvements in QOL included the presence of significant AF symptoms at baseline, shorter duration of AF and presence of SR at follow-up. Therefore, the authors concluded that although rate or rhythm control did not appear to influence QOL, patients with complaints of symptoms could derive some potential benefit

from rhythm control. This study adds to the literature suggesting that rate control is appropriate for many patients with AF, but highlights the fact that the decision to use rhythm control for certain patients should be individualized, based on symptoms at presentation.

Hagens VE, Vermeulen KM, TenVergert EM, et al. Rate control is more cost-effective than rhythm control for patients with persistent atrial fibrillation—results from the Rate control versus electrical cardioversion (RACE) study. *Eur Heart J* 2004;25:1542–9.

This paper describes a planned cost-effectiveness analysis of the RACE study, which demonstrated a similar rate of CV events in patients with persistent AF randomized to rate or rhythm control. In this analysis, a cost-minimization analysis was performed from the societal perspective. Cost savings per avoided end point was also calculated. Sensitivity analysis was performed by varying costs by 20% in either direction. Actual costs were used for most costs generated in study centers. Rhythm control was found to cost approximately \$1200 more than a rate control strategy. This translated to a savings of \$32,000 per end point avoided. The primary costs in the rhythm control arm were attributed to cardioversions, hospitalizations and drug expenditures. Costs were also evaluated in important subgroups and were found to be higher in women, patients greater than 70 years of age, and AF with underlying heart disease (versus patients with lone AF). It should be noted that although this analysis was performed from the societal perspective, costs of reduced productivity and lost work days were not considered. The authors attributed this to the fact that most patients were of “retirement age” and therefore, time off from work was not considered relevant. Therefore, the authors acknowledge that these data cannot be applied universally to all AF patients. Despite this limitation, this study is consistent with other literature supporting the economically favorable role of rate control in the management of AF.

Anticoagulation

ACTIVE Writing Group. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled

trial. *Lancet* 2006;367:1903–12.

The ACTIVE program is comprised of three separate trials, two of which were ongoing at the time of this publication (ACTIVE A and ACTIVE I). The ACTIVE W trial compared clopidogrel plus aspirin to oral anticoagulation therapy in the prevention of vascular events in patients with AF at a high risk for stroke. A total of 6706 patients were randomized to receive either an oral vitamin K antagonist (international normalized ratio [INR] between 2.0 and 3.0) or clopidogrel (75 mg) plus aspirin (75–100 mg) daily. The primary outcome of the study was the first occurrence of stroke (ischemic, primary hemorrhagic, or of uncertain type), non-central nervous system systemic embolism, myocardial infarction (MI), or vascular death. Subjects were enrolled between June 2003 and December 2005. However enrollment was reopened briefly in July 2005 due to lower than expected event rates. In August 2005, the study was ended early after the data safety monitoring board revealed clear evidence that oral anticoagulation is superior over clopidogrel plus aspirin. In the oral anticoagulation group, there were 164 primary outcome events compared with 234 events in the group of subjects receiving clopidogrel plus aspirin ($p=0.003$). Upon evaluation of individual components within the primary outcomes, the oral anticoagulant group had the lowest event rate. Of most significance was the advantage of oral anticoagulation therapy in the reduction of stroke ($p=0.001$) and non-central nervous system systemic embolism ($p=0.005$) events. This study accounted for the severity of stroke and the subjects receiving clopidogrel plus aspirin had more stroke events across all levels of severity. However, the RR of stroke decreased as the stroke severity increased indicating that oral anticoagulant therapy was more likely to prevent a less severe stroke ($p=0.027$). Major hemorrhage rates were similar in the two groups although more minor bleeds and total bleeds were seen in the clopidogrel group. Intracranial bleeds were more common in subjects receiving oral anticoagulation therapy. Authors state that more selective inclusion criteria may have contributed to the lower risk of stroke rates in both groups as compared to previously conducted studies.

Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer MA, Chrolavicius S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066–78.

The ACTIVE A study was part of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) series, which seeks to evaluate the role of clopidogrel plus aspirin for the prevention of stroke and other vascular events in patients with AF. The primary outcome of the study was any major vascular event and the major secondary outcome was stroke. The 7554 patients enrolled in this randomized, double-blind, multicenter and multi-country study were at an increased risk of stroke (CHADS2 score of ≥ 1) and were unsuitable candidates for oral vitamin K antagonists. All patients received aspirin 75–100 mg daily and were randomized to receive clopidogrel 75 mg (3772 patients) or placebo (3782 patients). The mean age of patients was 71 years and 58.2% were men. The mean CHADS2 score was 2.0. The primary endpoint occurred in 6.8% of patients receiving clopidogrel and in 7.6% of patients receiving placebo (relative risk [RR] 0.89; 95% CI, 0.81–0.98; $p=0.01$). Stroke occurred in 2.4% and 3.3% of patients in the clopidogrel and placebo groups, respectively (RR 0.72; 95% CI 0.62–0.83; $p<0.001$). Major bleeding occurred in 2% of patients receiving clopidogrel compared to 1.3% of patients in the control group (RR 1.57; 95% CI, 1.29–1.92; $p<0.001$), with the gastrointestinal tract being the most common site of hemorrhage. The reduction in the primary end point as seen in the study group was primarily due to a reduction in the rate of stroke. While there was a significant increase in the risk of major hemorrhage, the authors conclude that clopidogrel plus aspirin reduced the rate of vascular events among patients with AF at an increased risk of stroke in patients in whom vitamin K antagonists were unsuitable as compared to aspirin alone.

Rash A, Downes T, Portner R, et al. A randomized controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Aging* 2007;36:151–6.

This was a small, randomized, open-label prospective study that evaluated the risks and benefits of dose-adjusted warfarin (INR 2.0–3.0) and aspirin 300 mg in octogenarians. The primary outcome was a composite of the frequency of death, thromboembolism, serious bleed, and study withdrawal. Secondary outcomes included compliance, minor bleeding, and the amount of time in target INR range (only

in subjects receiving warfarin). Subjects were included if they were > 80 and < 90 years old, were ambulatory, and had permanent AF. Seventy-five subjects were followed every 3 months for one year. Thirty-six patients were randomized into the warfarin group and 39 into the aspirin group. Thirty subjects were enrolled into the compliance substudy and were prescribed 4 weeks of warfarin (n=17) or aspirin (n=13) dispensed in a medication event monitoring system vial. An adverse event was experienced by 33% of patients in the aspirin group and 6% of patients in the warfarin group (RR 6.0; 95% CI 1.5–24.8). Two subjects withdrew from the substudy. In the 4-week substudy, 96.4% of patients in the warfarin group and 100% of patients in the aspirin group were compliant. Thirteen percent (10/75) reported minor bleeds (6 in warfarin, 4 in aspirin; p=0.39) throughout the year. Subjects receiving warfarin were within the goal INR range 69.2% ± 17.2 of the time. Results of the study suggests that warfarin (INR 2.0–3.0) has a benefit over aspirin in this study population; however, it was not powered to detect the difference in benefit between the two groups in terms of thromboembolism. The Birmingham Atrial Fibrillation of the Aged (BAFTA) study protocol will address this issue. Authors concluded that warfarin is safe in this selected group of octogenarians.

Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. *Lancet* 2007;370(9586):493–503.

Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with AF. However, elderly patients are also at greater risk in developing complications (namely bleeding) with anticoagulants. The BAFTA study was designed to evaluate whether anticoagulants' benefit outweighs the increased risk of bleeding. Nine hundreds and seventy-three patients aged 75 years or over (mean age 81.5 years) with AF were randomly assigned to warfarin (INR 2–3) or aspirin (75 mg per day). Exclusion criteria of the study included rheumatic heart disease, major non-traumatic hemorrhage, intra-cranial hemorrhage, esophageal varices, active peptic ulcer disease, allergy to warfarin or aspirin, terminal illness, as well as any clinical reasons deemed by the

patients' primary care physicians that patients need to be on warfarin or aspirin therapy specifically. Duration of follow-up was a mean of 2.7 years. The primary endpoint was fatal or disabling stroke (ischemic or hemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. Twenty-four primary events were reported (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in the warfarin group and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in the aspirin group (annual risk 1.8% vs 3.8%, relative risk 0.48, 95% CI 0.28–0.80, p=0.003). Yearly risk of extracranial haemorrhage was 1.4% (warfarin) versus 1.6% (aspirin) (relative risk 0.87, 0.43–1.73; absolute risk reduction 0.2%, -0.7 to 1.2).

These data support the use of anticoagulation therapy for people aged over 75 who have AF and do not otherwise have contraindications or risk in taking warfarin.

Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007;100:1419–26.

The PETRO study was the first to evaluate dabigatran in patients with AF and to identify a safe dose of this drug as determined by bleeding and clinical events. The study outcomes were to determine if a dose-related bleeding incidence occurred and to collect pharmacodynamic data to assist in dose determination. Patients were randomized if they had AF and if they were considered high-risk patients for an embolic event. Inclusion criteria were AF with coronary artery disease at least one of the following: hypertension requiring treatment, diabetes mellitus, symptomatic HF or LV dysfunction, previous stroke or transient ischemic attack, or age > 75 years. The requirement for coronary artery disease was removed half way through recruitment due to difficulties identifying patients. The trial was composed of 502 patients into 10 treatment groups in a 6:9:9:4 stratified ratio; three doses of dabigatran (50, 150, and 300 mg twice daily) were evaluated in a 3 x 3 factorial design with no aspirin or 81- or 325-mg aspirin daily. Patients in the comparator group received warfarin. Dabigatran doses were assigned in a double-blinded but the assignment to aspirin and warfarin were done in open-label fashion. Due to

major hemorrhages in the group receiving dabigatran 300 mg twice daily plus aspirin (both 81- and 325-mg), the data and safety monitoring board decided to remove concomitant aspirin use. The mean age for those with a history of coronary artery disease was 70.9 ± 7.9 years and 68.0 ± 8.8 years for those without coronary artery disease. Major bleeding events were only experienced by patients in the group treated with 300 mg dabigatran twice daily plus aspirin and the incidence was significant when compared to 300 mg dabigatran alone ($p < 0.05$). Total bleeding events were more frequent in the 300 mg and 150 mg groups as compared to the 50 mg groups ($p = 0.0002$ and $p = 0.01$). Thromboembolic events occurred in the 50 mg dabigatran group only and the two highest doses suppressed D-dimer concentrations. Adverse events were more frequent in the dabigatran patients than those treated with warfarin. The most common adverse events included gastrointestinal disorders and general system disorders such as fatigue, edema, dizziness, headaches, and infections. Serious liver toxicity was not observed.

Antiarrhythmics

Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;360:668–78.

In this trial, also known as ATHENA, patients with paroxysmal or persistent AF were enrolled if they met at least one of the following criteria: ≥ 70 years old; arterial hypertension treated with at least two antihypertensives from different classes; diabetes mellitus; previous stroke, transient ischemic attack; or systemic embolism; increased left atrial diameter; and LVEF $\leq 40\%$. Due to low mortality rates over the course of the trial and in an attempt to enrich the risk profile of the overall study population, a protocol change excluded patients < 70 years old and included patients ≥ 75 years that were eligible regardless of risk factors. Patients were ineligible if they had New York Heart Association (NYHA) class IV HF. Patients ($n = 4628$) were enrolled while either in SR or in AF or atrial flutter and were randomly assigned in a 1:1 ratio to receive dronedarone 400 mg twice daily or placebo. The primary study end point was first hospitalization due to CV events or death from any cause. The mean age was 71.6 years and 46.9% were female. In patients who received dronedarone, 31.9%

experienced a primary end point event, including 29.3% with a CV event-related hospitalization and 2.6% who died. In the placebo group, 39.4% experienced a primary end point event, 36.9% of which included a CV event-related hospitalization and 2.5% who died. The HR in the dronedarone group was 0.76 (95% CI, 0.69 to 0.84; $p < 0.001$). The authors stated that the reduction in the number of CV-related hospitalizations was influenced by a reduction in the number of hospitalizations for AF. They concluded that dronedarone significantly reduced the risk of hospitalization due to CV events or death in patients with paroxysmal or persistent AF or atrial flutter.

Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study. *J Cardiovasc Electrophysiol* 2010;21:597–605.

This comparative, randomized, double-blind, parallel-group, multicenter, multi-country short-term study compared dronedarone and amiodarone in order to determine the benefit/risk ratio. In this intention-to-treat analysis, patients received study drug while still in AF and unsuccessful electrical cardioversion plus no spontaneous or electrical conversion to SR was considered treatment failure. Patients were eligible for inclusion if they were ≥ 21 years with AF for > 72 hours and if cardioversion and AAD treatment were indicated. Patients were randomized in a 1:1 ratio to dronedarone 400 mg twice daily or amiodarone 600 mg daily for 28 days and then 200 mg for at least 6 months. Electrical cardioversion was to be performed between days 10 and 28 if spontaneous conversion to SR did not occur by then. The primary efficacy end point was time to first AF recurrence or premature study drug discontinuation. There were several prespecified main safety end points including time to any first main safety endpoints component gastrointestinal events, and time to first event for each safety endpoint component. Main safety endpoint components include the occurrence of thyroid, hepatic, pulmonary, neurologic, skin, eye or gastrointestinal specific events, or premature study drug discontinuation following an adverse event. Demographics of the 504 patients randomized were well balanced. The mean age

was 64 ± 10.7 years and 20% were ≥ 75 years of age. After 12 months of treatment, the incidence of the composite primary end point was 75.1% and 58.8% in the dronedarone and amiodarone groups, respectively ($p < 0.001$) and was mainly driven by AF recurrence which was more frequent in the dronedarone (63.5%) than in the amiodarone (42%) group. The rate of premature drug discontinuation was less frequent in the dronedarone group (10.4%) than in the amiodarone group (13.3%). The incidence of the main safety end points was 39.3% in the dronedarone group compared to 44.5% in the amiodarone group ($p = 0.129$). This was driven by fewer thyroid, neurologic, skin, and ocular events while more patients experienced higher gastrointestinal events with dronedarone. There was a trend towards less premature drug discontinuation due to adverse events in the dronedarone group. Dronedarone was less effective than amiodarone in decreasing AF recurrence but had a better safety profile.

Treatment Guidelines

Singer DE, Albers GW, Dalen JE, et al. Antithrombotic Therapy in Atrial Fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* June 2008; 133: 546S–592S.

The eighth American College of Chest Physicians (ACCP) Conference provides evidence-based guidelines in the management of thromboembolic disorders using a grading system that is consistent with all ACCP guidelines; the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. The strength of the recommendation depends on risks, burdens, and costs to the patient. Recommendations considered to be a strong recommendation is labeled Grade 1 and a weaker recommendation is labeled Grade 2. The guidelines provide level of results based on the design in which clinical data was gathered. High-quality, moderate-quality, or low-quality evidence is labeled with A, B, or C, respectively. The authors will “recommend” when a recommendation is strongly graded (i.e., Grades 1A, 1B, and 1C) and “suggest” when a recommendation is weaker (i.e., Grades 2A, 2B, and 2C). The chapter designated to atrial fibrillation (AF) provides recommendations on anticoagulation or antithrombotic therapy in patients with AF, atrial flutter, valvular heart disease, management of AF following cardiac

surgery, and elective cardioversion. Therapy recommendations for AF and atrial flutter are largely dependent on past medical history and the following risk factors for future ischemic stroke: 1) age > 75 years; 2) history of hypertension; 3) diabetes mellitus; and 4) moderately or severely impaired left ventricular systolic function and/or heart failure. For example, it is recommended that patients with AF, including paroxysmal AF, or atrial flutter with a past medical history of ischemic stroke, transient ischemic attack, or systemic embolism or with two or more risk factors for future ischemic stroke should receive long-term anticoagulation with an oral vitamin K antagonist with a targeted INR goal of 2.5 (range 2.0 to 3.0).

Douketis JD, Berger PB, Dunn AS, et al. The Perioperative Management of Antithrombotic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:299S–339S.

The eighth American College of Chest Physicians (ACCP) Conference provides evidence-based recommendations on the perioperative management of antithrombotic therapy in patients currently receiving vitamin K antagonists, receiving bridging anticoagulation, receiving antiplatelet therapy, requiring dental, dermatologic, or ophthalmologic procedures, and requiring urgent surgical or other invasive procedures. These recommendations outline when therapy with oral vitamin K antagonists or antiplatelet agents should be stopped prior to a procedure, when therapy should resume, when bridging with a low-dose or therapeutic-dose subcutaneous low molecular weight heparin or intravenous unfractionated heparin should be considered, and when oral vitamin K should be administered. The guidelines recommend that patients requiring temporary interruption of vitamin K antagonist therapy should discontinue use of these agents five days prior to a procedure and resume therapy 12 to 24 hours after the procedure when adequate hemostasis has occurred. Patients requiring a disruption in antiplatelet therapy with aspirin or clopidogrel are recommended to discontinue use seven to ten days prior to procedure and to resume therapy approximately 24 hours post-procedure when adequate hemostasis has occurred. In the event that subcutaneous low molecular weight heparin be deemed appropriate, the guidelines recommend administering the last dose 24 hours prior to the procedure at half of the total daily

dose and resuming the pre-procedure regimen approximately 24 hours post-procedure. The chapter concludes with an overview of the types of dental, dermatologic, and ophthalmologic procedures in which antithrombotic therapy modifications must be considered and how to manage patients who require reversal of anticoagulation or antiplatelet effects in order to proceed with an urgent, invasive surgical procedure.

Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Circulation* 2006;114:e257–e354.

The committee that revised the 2001 guidelines was comprised of members representing the American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology with collaborative efforts from the European Heart Rhythm Association and the Heart Rhythm Society (HRS). The familiar format for the classification of recommendations (Class I-III) and level of evidence available (A-C) was used to provide evidence-based recommendations. The guidelines have been rearranged slightly since the last release. Initial content defines and classifies the types of atrial arrhythmias and provides epidemiology data. Brief explanations of disease progression, diagnosis, comorbidities and impact on QOL are provided before listing pharmacological and nonpharmacological management strategies for the prevention and treatment of AF. Seven strategies are listed for the overall management of a patient upon diagnosis, including: (1) type and duration of AF, (2) severity and type of symptoms, (3) associated CV disease, (4) patient age, (5) associated medical conditions, (6) short- and long-term treatment goals, and (7) pharmacological and nonpharmacological therapeutic options. Treatment algorithms provide pharmacotherapy guidance for prevention of thromboembolism and rate/rhythm control decisions. The role of using angiotensin-converting enzyme (ACE) inhibitors for primary prevention and decreasing complications from AF is reported. Drug therapy

summaries are based solely from data derived from human studies with clinically approved agents in North America and/or Europe. The guidelines also highlight special circumstances that may identify those patients at risk for developing AF and treatment considerations in these populations. An example is the role for prophylaxis with AADs prior to a patient scheduled for cardiac surgery. These guidelines are available on the internet at the following websites: www.acc.org, www.americanheart.org, www.escardio.org, and www.hrsonline.org.

ATRIAL FIBRILLATION – NON-PHARMACOLOGIC MANAGEMENT

Oral H, Pappone C, Chugh C, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;354:934–41.

This study was one of the first randomized trials comparing pulmonary vein isolation with a control group. Overall, 146 patients with chronic AF (paroxysmal or persistent) were randomized to amiodarone plus two cardioversions during the first 3 months in the study or to these procedures plus pulmonary vein isolation (circumferential) catheter ablation. The use of amiodarone as a comparator in ablation studies is reasonable since a previous trial (Canadian Trial of Atrial Fibrillation) found amiodarone more effective than either sotalol or propafenone in maintaining SR in AF. In this study with a 12-month follow-up, 32% of subjects receiving ablation had a repeat procedure due to recurrent AF or atrial flutter but 74% of subjects were ultimately free of AF without the need for AADs after the 3 months which was better than the 58% in the control group. The symptom severity score was lower in the group receiving catheter ablation (59% reduction; $p < 0.001$) as well as suggesting benefits in QOL with maintenance of SR.

Early MJ, Abrams DJR, Staniforth AD, Sporton SC, Schilling RJ. Catheter ablation of permanent atrial fibrillation: medium term results. *Heart* 2006;92:233–8.

This study focused on patients ($n=42$) with permanent AF who could not be maintained in SR even on chronic AAD therapy. In this study, pulmonary vein isolation plus additional ablation lines from the pulmonary vein to the mitral valve, along the roof of the left atrium, and along the tricuspid valve to the inferior vena cava were

made. The ultimate success rate (freedom from AF) was 76% but 31% of subjects needed AADs to maintain rhythm control. Maintenance of SR after a first, second, and third procedure was 36%, 58%, and 71%. This study suggests that a more rigorous ablation procedure lasting almost 6 hours can be effective in permanent AF although multiple procedures and concomitant AADs might be needed.

Oral H, Ozaydin M, Good E, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. *Circulation* 2006;114:759–65.

This was a noncontrolled assessment of thromboembolic events in 755 consecutive patients undergoing left atrial radiofrequency catheter ablation for paroxysmal or persistent AF. In this evaluation, all subjects were anticoagulated for ≥ 3 months with warfarin. While this recommendation is not backed up by data, it is known that patients with chronic AF do not regain contractile atrial function for a period of time even after normal electrical activity is restored. As such, even clinical success might still be associated with a clotting risk. In this study, 56% of subjects had ≥ 1 risk factor for stroke. Overall, 0.9% of patients had a thromboembolic event within 2 weeks and 0.2% of patients had an event between 6–10 months after ablation. Both of the patients with late thromboembolic event were still on warfarin at the and one was still in AF at the time of the event. This study shows that even in the year 2006, the thromboembolic event rate remains at 1.1%.

Da Costa A, Thevenin J, Roche F, et al. Results from the Loire-Ardeche-Drone-Isere-Puy-de-Dome (LADIP) trial on atrial flutter, a multicenter prospective randomized study comparing amiodarone and radiofrequency ablation after the first episode of symptomatic atrial flutter. *Circulation* 2006;114:1670–2.

While much of the literature has focused on AF ablation, patients with atrial flutter might also benefit from this procedure since ectopic foci are also a source of atrial flutter. This is a multicenter trial where 104 subjects were randomized to radiofrequency catheter ablation or cardioversion and amiodarone therapy and then followed-up for approximately 13 months. The recurrence of atrial flutter was 3.8% in the ablation group as compared to 29.5% in the amiodarone group ($p < 0.0001$). The authors

downplayed the non-significant elevation in AF occurrence (25% vs. 18%, $p = 0.30$) in the ablation group, but with a study of this size, they might not have had power to detect a significant increase in this parameter. Larger studies need to be conducted to determine if this increase in AF is artifact or a real phenomenon.

Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:32–8.

This is the most recent survey of catheter ablation use for treating AF. Of 182 centers that responded, 85 centers reported performing catheter ablation on an aggregate of 20,825 procedures on 16,309 patients between 2003 and 2006 (median of 245 procedures per center). All centers performed catheter ablation for paroxysmal AF, 85.9% and 47.1% of centers also performed catheter ablation for persistent AF and longstanding AF (formerly known as permanent AF), respectively. Over a median of 18 months of follow-up (ranging from 3–24 months) with 1.3 procedures being performed per patient, a median of 70% of patients were asymptomatic without concomitant AADs and another 10% became asymptomatic after use of previously ineffective AADs. This is an update of a survey conducted from 1995 to 2002 where the median number of procedures performed annually was only 37.5. In addition, in the previous survey, only 53% and 20% of centers performed catheter ablation for persistent and longstanding AF, respectively. This most recent survey shows a marked expansion in the number of centers performing catheter ablation and the number of patients being treated with this procedure. Survey data is not as reliable as controlled trial data when assessing efficacy but it is important to communicate that approximately every third patient will need a subsequent catheter ablation procedure to achieve the results noted above.

Wilber DJ, Pappone C, Neuzil, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;303:333–40.

In this multicenter trial (also known as the ThermoCool AF trial), patients ($n = 167$) who had at least three episodes of AF over the past 6 months and failed at least one AAD in the past were randomized in an unblinded fashion to

receive catheter ablation or AAD antiarrhythmic drug therapy and followed-up for 9 months. At the end of the trial, 66% of patients in the catheter ablation group and 16% of patients treated with AADs were free of AF (HR 0.30; 95% CI 0.19-0.47). Major 30 day adverse events occurred less frequently in the catheter ablation group than in the AAD group (4.9% vs. 8.8%). Quality of life also significantly improved in the catheter ablation group when compared to AAD therapy (SF-36 mental $p < 0.001$, SF-36 physical $p < 0.001$, symptom frequency $p < 0.001$, symptom severity $p < 0.001$). This is the first major multicenter study to directly compare catheter ablation to AAD therapy. It shows that when initial AAD therapy has failed, catheter ablation is superior to other AAD options. However, amiodarone is frequently employed after other AADs fail because it is superior to sotalol and propafenone in maintaining SR. Allowing the use of amiodarone at the physician's discretion would have been a more fair comparison.

Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;6:599–602.

This was a meta-analysis of 6 randomized controlled trials ($n=693$) comparing catheter ablation to medical therapy. At 12 months, 77% of patients receiving catheter ablation were free of AF compared to 29% of patients receiving medical therapy (OR 9.74; 95% CI 3.98 to 23.87) at 12 months. Hospitalization over 12 months was also significantly reduced in the catheter ablation group [14 vs. 93 hospitalizations per 100 person-years; rate ratio 0.15 (0.10 to 0.23)]. This meta-analysis was important because several previous trials evaluating catheter ablation were not adequately powered to evaluate these end points. This meta-analysis did not take into account the aforementioned multicenter ThermoCool AF trial but the results are congruent.

Di Biase L, Wang Y, Horton R, et al. Ablation of atrial fibrillation utilizing robotic catheter navigation in comparison to manual navigation and ablation: single center experience. *J Cardiovasc Electrophys* 2009;20:1328–35.

Like robotic surgery, catheter ablation can now be robotically assisted. This was a prospective observation study of 390 consecutively enrolled

patients with symptomatic and drug resistant AF. The success rate was similar between the robotic surgery and manual groups (85% vs. 81%; $p=0.264$) but the fluoroscopy (targeted X-ray) time was lower for the robotic surgery than the manual ablation group (48.9 ± 24.6 vs. 58.4 ± 20.1 minutes). Patients were not randomized in this evaluation and there may be patient or electrophysiologist differences that might bias these results. The results were not controlled for using multivariate analyses. However, even with these inherent biases, this is the first large scale comparison of robotic versus manual catheter ablation and yield useful interim results.

Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;16:1160–5.

An alternative to focal or pulmonary isolation ablation to try and cure AF is to ablate the atrioventricular (AV) node. This is to prevent depolarization waves from the fibrillating atria from reaching the ventricles. In this procedure, the AV node is ablated and a pacemaker is inserted to pace the ventricles at a regular rate. While this ablation technique can be a replacement for chronic negative dromotropic therapy with β -blockers, nondihydropyridine CCBs, or digoxin, use of AV nodal ablation does not obviate the need for chronic anticoagulation since the patient remains in AF. Chronic right ventricular pacing (the standard pacing employed after AV nodal ablation) has been shown to cause dissynchrony between the left and right ventricles (the ventricles depolarize and contract at different times). In patients with dissynchrony and HF, the use of biventricular pacing is shown to improve patient symptoms. However, whether biventricular pacing would be of benefit after AV nodal ablation has not been established. In this study, 184 patients undergoing AV nodal ablation were randomized to receive subsequent right ventricular or biventricular pacing. Six months after ablation, those with biventricular pacing had better improvements in 6-minute walking times (31% improvement vs. 24%; $p=0.04$) and LVEF ($46 \pm 13\%$ vs. $41 \pm 13\%$, $p=0.03$) but no differences in QOL when compared to those who received right ventricular pacing. Patients with LV dysfunction and those with class II or III HF received a majority of the benefits from biventricular pacing. This may be because ventricular dissynchrony is particularly detrimental in subjects with lower maximum

pumping capacity. It appears that subjects with LV dysfunction or mild to moderate HF should be considered for biventricular pacing after AV nodal ablation.

Pappone C, Santinelli V. Catheter ablation should be performed in asymptomatic patients with Wolff-Parkinson-White syndrome. *Circulation* 2005;112:2207–15.

In a normal heart, the depolarization of the sinoatrial node spreads throughout the atria and is held by the AV node for a period before being released into the ventricles. Wolff-Parkinson-White (WPW) syndrome occurs when there is a bypass tract of electrically active tissue connecting the atria with the ventricles. While the vast majority of the ventricles are ultimately depolarized by the wave of depolarization that leaves the AV node, a portion of the ventricle is depolarized via the bypass tract and causes the QRS complex to have a sloping upstroke called a delta wave rather than a crisp upstroke. In this review article, the authors demonstrate that the risk of sudden death due to ventricular fibrillation (VF) is increased in patients with WPW and in some cases, sudden death is the first symptom the patients ever experience. A full summary of the historical perspective of WPW and the mechanism underlying VF generation in WPW was given in this review. However, the portion of the review that is most helpful centers around the benefits of ablation in WPW patients. By ablating the electrically active bypass tract tissue, WPW is curable. The use of radiofrequency catheter ablation is commonly used in patients with symptomatic WPW but its use in asymptomatic patients is not as well established. The authors describe two studies conducted by the same research group in asymptomatic high-risk subjects showing dramatic reductions in the risk of arrhythmic events [(Study 1: 7% incidence of arrhythmic events with ablation vs. 77% with control; $p < 0.001$); (Study 2: 5% incidence of arrhythmic events with ablation vs. 44% with control; $p = 0.01$)]. By pooling previous data, the authors suggest that high risk patients with ablation have a risk of arrhythmic events that approximates that of a low risk population over a 48 month follow-up period and both of these groups have a greater chance of remaining asymptomatic than high risk control patients (log rank $p < 0.001$). Using a risk stratification technique to identify asymptomatic but high risk subjects is intriguing but needs further verification in a single

adequately powered study before it can be commonly recommended.

ATRIAL FIBRILLATION - POST-CARDIOTHORACIC SURGERY

Coleman CI, Perkeron KA, Kluger J, Gallagher R, Horowitz S, White CM. Impact of prophylactic postoperative β -blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. *Ann Pharmacother* 2004;38:2012–6.

Over 750,000 cardiothoracic surgeries (CTS; i.e. coronary artery bypass and/or heart valve surgery) are performed annually in the United States. Approximately 30-40% of subjects get AF post-CTS but most bouts are self-limiting and do not result in negative consequences. In 27 studies encompassing 3840 subjects, β -blockers reduced post-CTS AF incidence significantly but these studies did not evaluate the impact of β -blockers on other end points such as mortality, hemodynamic instability, and length of stay. That was why the impact of prophylactic β -blockers on post-CTS AF, length of stay, and clinical end points were studied in this prospective, propensity score matched cohort evaluation. Patients ($n = 1660$) undergoing CTS at a single institution between 1999 and 2003 and not receiving β -blockers were matched 1:1 (matched for age > 70 years, valvular surgery, AF history, gender, preoperative digoxin, and preoperative β -blockers) with subjects receiving prophylactic β -blockade. β -blocker use not only reduced the incidence of post-CTS AF (23.5% vs. 28.4%, $p = 0.02$) but also reduced length of stay (10.2 ± 11.4 vs. 12.4 ± 15.7 days; $p = 0.001$). There were more than 50% reductions in the development of pulmonary edema, need for intra-aortic balloon pump support, or death ($p < 0.01$ for all analyses). This study helps to show that preventing post-CTS AF with β -blockers can impact length of stay and clinical events as well.

Gillespie EL, Coleman CI, Sander S, et al. Effect of prophylactic amiodarone on clinical and economic outcomes after cardiothoracic surgery: a meta-analysis. *Ann Pharmacother* 2005;39:1409–15.

Amiodarone is another potential prophylactic strategy to prevent post-CTS AF. While 15 trials had been conducted evaluating the impact of amiodarone on post-CTS AF, the studies were too small to evaluate harder end points. In a meta-analysis of these 15 trials encompassing 2941 patients, amiodarone was associated with a

reduction in AF (OR 0.50; 95% CI 0.42–0.60), stroke (OR 0.47; 95% CI 0.23–0.96), length of stay (OR -0.73 days; 95% CI -0.95 to -0.51 days), and total hospital costs (OR -\$1619; 95% CI -\$3395 to -\$156). This meta-analysis suggested that there were reductions in clinical end points and total costs with amiodarone induced post-CTS AF suppression.

DiDomenico RJ, Massad MG. Pharmacologic strategies for prevention of atrial fibrillation after open heart surgery. *Ann Thorac Surg* 2005;79:728–40.

This is a review article that assessed the literature support for numerous prophylactic strategies to decrease post-CTS AF. While numerous drug strategies have been evaluated, only β -blockers, amiodarone, and sotalol have been established rigorously enough to employ in standard practice. The authors propose an algorithm suggesting that β -blockers be combined with amiodarone for any patient with a post-CTS AF risk factor. The amiodarone regimens that were selected were those used in the Atrial Fibrillation Suppression Trials (AFIST) I and II. While many studies of post-CTS AF prevention with amiodarone have been conducted, AFIST I and II utilized amiodarone regimens that could be employed in patients with elective CTS and emergent CTS and they had high baseline utilization with β -blockers suggesting that the benefits were over and above that with β -blockers. If this combination strategy could not be used, monotherapy with sotalol 120–160 mg daily could be started as an alternative. In people without post-CTS risk factors, the authors still recommended β -blockers and then based on non-CTS data, suggested that renin angiotensin aldosterone system antagonists could be tried. However, the mechanism by which chronic ACE inhibitor or ARB therapy might reduce AF has not been fully determined and may be due to their ability to prevent pathogenic left atrial remodeling. If this is the mechanism, these agents would not be effective when given on a short term basis.

Mitchell LB, Exner DV, Wyse DG, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair. *JAMA* 2005;294:3093–3100.

The Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization (PAPABEAR) trial was the

largest of the post-CTS prophylactic amiodarone trials to date with 601 patients enrolled. Oral amiodarone (10 mg/kg/day) or placebo was started 6 days before surgery and continued on the day of surgery and for 6 postoperative days (13 days total). The important results were not that PAPABEAR found that the use of amiodarone decreased the risk of post-CTS AF (HR 0.52; 95% CI 0.34–0.69) but that it decreased AF in patients who received (HR 0.58; 95% CI 0.34–0.99) and did not receive (HR 0.40; 95% CI 0.22–0.71) prophylactic β -blockers. This means that instead of choosing β -blockers or amiodarone, the combination was clearly associated with additional benefits over either agent alone. Like in the original AFIST, the use of amiodarone in PAPABEAR was associated with a reduction in ventricular arrhythmias (0.3% vs. 2.6%, $p=0.04$) as well. While this was the best study of preoperative plus postoperative amiodarone prophylaxis conducted to date, the study is limited in that patients had to receive 6 days of preoperative loading which would exclude the subjects who required emergent CTS (CTS scheduled either the day after or day of their cardiac catheterization). The aforementioned AFIST I and AFIST II studies did have regimens that accounted for these emergent surgery patients.

Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery. *Circulation* 2006;114:1455–61.

While sympathetic activation is one potential mechanism of post-CTS AF, other mechanisms such as fluid overload/atrial stretch and inflammation may also contribute. The Atorvastatin for Reduction of MYocardial Dysrhythmia After Cardiac surgery study (ARMYDA-3) evaluated the impact of high intensity statin therapy on post-CTS AF. In this study, 99 patients in Italy received atorvastatin 40 mg or placebo starting 7 days before surgery. Atorvastatin therapy reduced the incidence of post-CTS AF (35% vs. 57%; $p=0.003$) and reduced length of stay (6.3 ± 1.2 vs. 6.9 ± 1.4 days; $p=0.001$) but the study was underpowered to look for other major cardiac or cerebrovascular events. While this is an interesting and well-conducted trial, it has low external validity. Currently, most patients in the United States undergoing CTS already receive statin therapy so the impact of higher versus lower intensity statin

therapy would be a more useful clinically evaluation than statin versus placebo. The 57% incidence of post-CTS AF in the placebo group is much higher than that seen in the United States suggesting that the benefits in this study might be muted in a United States population. Preoperative use of prophylactic statin strategy was required so patients with emergent surgery would not be able to receive therapy. Even with these limitations, statin or anti-inflammatory suppression of post-CTS AF is a very promising area for future research and the ARMYDA-3 trial has sparked this interest.

White CM, Sander S, Coleman CI, et al. Impact of epicardial anterior fat pad retention on post-cardiothoracic surgery atrial fibrillation incidence: the Atrial Fibrillation Suppression Trial III (AFIST III). *J Am Coll Cardiol* 2007;49:298–303.

The anterior fat pad is located near the aortic root and is innervated with parasympathetic nerve fibers. It is commonly dissected in CTS to more fully expose the aortic root. A promising strategy to prevent post-CTS AF has been the retention of the anterior fat pad. A previous study of 55 patients had showed that anterior fat pad retention was associated with a reduction in post-CTS AF; however, this was a secondary end point. In the AFIST III, 180 patients undergoing coronary artery bypass surgery (heart valve surgery requires AFP removal so valve patients were excluded) were randomized to anterior fat pad maintenance or anterior fat pad removal. Routine prophylaxis with β -blockers and amiodarone was allowed. Anterior fat pad maintenance did not reduce post-CTS AF incidence (34.8% vs. 35.2%; $p=0.950$) or total hospital costs (data as medians with 25% and 75% percentile ranges: \$22,940 [17,629; 29,274] vs. \$23,866 [18602; 30370]; $p=0.647$) but was associated with higher heart rate variability (SD of normal-to-normal RR intervals (SDNN): 31.7 ± 24.6 vs. 22.7 ± 8.3 , $p=0.05$ and SD of all 5-min mean RR intervals (SDANN5): 17.1 ± 11.9 vs. 10.1 ± 5.5 , $p=0.003$) than anterior fat pad removal suggesting preserved parasympathetic tone. This study showed that while anterior fat pad maintenance preserved parasympathetic tone, it was not associated with a reduction in post-CTS AF. Whether it would have provided benefits in a population that did not have sympathetic suppression with β -blockers and amiodarone is not known. However, it seems that anti-inflammatory and biatrial pacing

strategies are better potential strategies for future research.

VENTRICULAR ARRHYTHMIAS

Acute Management

Sagalyn E, Band RA, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: Review and compilation of recent experiences. *Crit Care Med* 2009;37(7 Suppl):S223–6.

The authors performed a literature search for reports on therapeutic hypothermia after cardiac arrest in adults. They included 13 nonrandomized cohort studies that were published after 2002 when the results of the Hypothermia After Cardiac Arrest (HACA) study were published. This real world assessment of therapeutic hypothermia showed similar survival and neurological outcomes as larger, randomized trials. Studies with historical controls compared survival and outcome and showed approximately 2–3-fold improvements in survival and neurological outcomes. Notably, those reports without historical control data showed similar survival-to-hospital discharge rates (59% vs. 65%) and neurological outcomes in the therapeutic hypothermia groups (45% vs. 47%) as those studies with historical controls. Adverse event reporting among the 13 studies was variable and therefore not statistically assessed. The authors included only adverse events that were reported most frequently, including, pneumonia, sepsis, arrhythmias, and bleeding. Patients in therapeutic hypothermia cohorts experienced similar adverse events as those considered as historical controls. The authors noted a need for a consensus of data reporting to make more meaningful comparisons to further enhance therapeutic hypothermia to improve patient outcomes.

Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008;359:21–30.

The debate of the value of vasopressin in cardiac arrest continues in this large, randomized, clinical trial performed in France. Based on a small subgroup analysis suggesting promise of combined administration of vasopressin and epinephrine in patients with refractory cardiac arrest, the authors conducted a study in 2894 out-of-hospital cardiac arrest adults presenting with VF, pulseless electrical

activity (PEA), or asystole. Patients received either 1 mg of epinephrine and 40 units of vasopressin or 1 mg of epinephrine and saline placebo in separate intravenous (IV) injections. All medications were followed by a 20 mL normal saline flush. If return of spontaneous circulation (ROSC) did not occur within 3 minutes, the same combination was administered again. Thereafter, after another 3 minutes, patients were given open-label epinephrine at the discretion of the physician. Only amiodarone or fibrinolytics could also be administered. The primary end point was survival to hospital admission, defined as a palpable pulse and blood pressure. Secondary end points were ROSC (defined as return of palpable pulse and blood pressure for at least 1 minute), survival to hospital discharge, good neurological recovery (defined as cerebral-performance category 1 = conscious with normal function or only slight disability), and 1-year survival. The two groups were similar except more men were in the combination group ($P=0.03$). There were no differences in the primary end point or any of the secondary end points between the combination-therapy and the epinephrine-only groups. There were no significant differences among patients presenting with VF or asystole. However, a post hoc subgroup analysis showed that patients presenting with PEA had a higher rate of survival to hospital discharge in the epinephrine-only group (5.8% vs. 0%, $P=0.02$). Interestingly, 17% of admitted patients underwent therapeutic hypothermia during the first 24 hours demonstrating less neurologic impairment compared to those not treated with therapeutic hypothermia; however this intervention was not randomized.

Olasveengen TM, Sunde K, Brunborg C, et al. Intravenous drug administration during out-of-hospital cardiac arrest. *JAMA* 2009;302:2222–9.

This prospective, randomized controlled trial of IV drug administration during out-of-hospital cardiac arrest was done because there are no studies showing improved survival to hospital discharge with any of the drugs routinely used during advanced cardiac life support (ACLS). Patients were randomized to either IV drugs during ACLS or no IV drugs during ACLS. In the latter group, IV access was established 5 minutes after ROSC, and drugs could be administered there if needed. The primary end point was survival to hospital discharge. Secondary outcomes were 1-year survival, survival with

favorable neurological outcome, hospital admission with ROSC, and quality of cardiopulmonary resuscitation (CPR). Based on observational studies, it was predicted that survival would be twice as high in those not receiving epinephrine, requiring 900 patients to provide a power level of 91.4%. There were 851 of 946 eligible patients randomized with 418 in the IV group and 433 in the no IV access group. Both groups had similar CPR quality. In the IV group, 44 (10.5%) survived to hospital discharge vs. 40 (9.2%) in the no IV group (OR, 1.16; 95% CI, 0.74–1.82; $P=0.61$). Survival with favorable neurological outcome was not statistically different. Short-term survival was better in the IV group than in the no IV group with ROSC occurring in 40% vs. 25% (OR, 1.99; 95% CI, 1.48–2.67; $P<0.001$), admission to the hospital occurring in 43% vs. 29% (OR, 1.81; 95% CI, 1.36–2.40; $P<0.001$), and admission to the intensive care unit occurring in 30% vs. 20%, respectively (OR, 1.67; 95% CI, 1.22–2.29; $P=0.002$). However, there were no significant differences in being discharged alive or 1-year survival between groups. In patients presenting with VF or pulseless ventricular tachycardia (VT), there were no differences in short or long-term outcomes. However, in the subgroup with asystole or PEA, the ROSC rate was three-fold higher in the IV group ($P<0.001$). Again, there was no difference in long-term outcomes. This study did not show that IV interventions and administration of drugs was harmful in patients with out-of-hospital cardiac arrest, however with no improvement in survival to discharge, future evaluation of new pharmacologic agents should be undertaken.

Stiell IG, Walker RG, Nesbitt LP, et al. BIPHASIC Trial: A randomized comparison of fixed lower versus escalating higher energy levels for defibrillation in out-of-hospital cardiac arrest. *Circulation* 2007;115:1511–7.

The 2005 AHA guidelines endorsed the biphasic waveform defibrillator as the preferred technology for patients with shockable lethal arrhythmias. Biphasic defibrillators are more effective in terminating VF compared to the traditional monophasic waveform defibrillators. The optimal energy level for first and subsequent biphasic shocks has not been clearly established. This study was a triple-blinded, randomized controlled trial comparing a fixed lower energy (150-150-150 joules [J]) regimen to an escalating higher energy (200-300-360 J) regimen in

patients who suffered out-of-hospital cardiac arrest requiring defibrillation. The primary outcome of this study was the successful termination of VF to an organized rhythm within 60 seconds. Clinical outcomes included ROSC, survival for 1 hour, survival for 24 hours, and survival to hospital discharge. There were no differences in the primary outcome between groups for the first shock received (38.4% and 36.7%; $P=0.92$). However, for the 48% of patients who required multiple shocks due to either failed termination or recurrence of VF, there was a statistically significant difference between groups (24.7% and 36.6%; $P=0.035$; 95% CI, 1.2–24.4). This study was underpowered and therefore secondary survival outcomes were not different between the two groups. Adverse outcomes such as elevations of troponin were similar in both groups. Larger clinical trials are needed to determine whether the electrical benefits of an escalating higher-energy regimen in this study translate to improved clinical outcomes of survival to discharge.

Sayre MR, Berg RA, Cave DM, et al. Hands-only (compression-only) cardiopulmonary resuscitation: A call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest. A science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. *Circulation* 2008;117:2162–7.

Three years after the AHA Emergency Cardiovascular Care (ECC) scientific guidelines were published, the AHA published a science advisory to clarify recommendations for CPR for bystanders who witness an adult out-of-hospital cardiac arrest and to summarize research published since 2005. The 2005 guidelines state that “laypersons should be encouraged to do compressions-only CPR if they are unable or unwilling to provide rescue breaths (Class IIa), although the best method of CPR is compressions coordinated with ventilations.” Multiple animal studies evaluating compressions only yielded varying results except in asphyxiated precipitated cardiac arrests which clearly demonstrated benefit with rescue breathing as a component of CPR. Three nonrandomized observational studies in humans were published since 2005 and none demonstrated negative outcomes on survival with compressions-only compared to conventional CPR. The advisory also addresses ways to reduce barriers to bystander action and

describes that bystanders can use “hands only” or conventional CPR in adults who experience witnessed out-of-hospital cardiac arrest. The goal to increase bystander CPR and to highlight the need for further research is the ultimate goal of this advisory.

Callaway CW, Hostler D, Doshi AA, et al. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol* 2006;98:1316–21.

In this trial, 325 adult nontraumatic, out-of-hospital cardiac arrest victims who had already received at least one dose of epinephrine were randomized to receive placebo (plus standard treatment) or 40 units of vasopressin (plus standard treatment) as soon as possible after the first dose of epinephrine. Primary outcomes were ROSC at any time and the presence of pulses at hospital admission and were similar between the vasopressin and placebo groups. Multivariable logistic regression demonstrated that ROSC and a pulse at hospital arrival was associated with witnessed collapse and a shorter dispatch-to-arrival interval but not to vasopressin administration during the arrest. Similarly, there were no differences between groups for the secondary outcome of total duration of survival. This is another study failing to demonstrate the benefits of vasopressin in out-of-hospital cardiac arrest patients.

Goldberger JJ, Suacius H, Schaechter A, et al. Effects of statin therapy on arrhythmic events and survival in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2006;48:1228–33.

The pleiotropic effects of statins in patients with nonischemic dilated cardiomyopathy were investigated in this substudy of the Defibrillators In Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial. This was a randomized, prospective investigator-initiated study that evaluated patients with a LVEF $\leq 35\%$, history of symptomatic HF, and the presence of one of the following within the past 6 months: nonsustained VT or an average of 10 ventricular premature beats (VPBs) per hour. Patients were randomized to standard therapy for HF with or without an implantable cardioverter-defibrillator (ICD). In this trial, 85% and 90% of patients were receiving β -blockers and ACE inhibitors, respectively. The primary end point was death from any cause with a secondary analysis of sudden arrhythmic death. Of the 458 patients

enrolled, 110 patients on statins at the time of their first event (death or resuscitated cardiac arrest) or at the end of the trial were compared to those not on statins (n=348). Five deaths occurred in the statin group (4.6%) versus 64 deaths (18.4%) in the group not receiving statins (p<0.01). The unadjusted HR was 0.22 (95% CI 0.09–0.55; p=0.001). There was only one arrhythmic sudden death (0.9%) in the statin group versus 18 in the patients not on statins (5.2%; p=0.04). The unadjusted HR was 0.16 (95% CI 0.022–1.21; p=0.08). Of the 229 patients who received an ICD, 56 were on statins at the time of their first appropriate shock or end of trial. Statistically more patients in the no-statin group were receiving ACE inhibitors or ARBs (96.5% vs. 89.3%; p=0.03). The group receiving statins experienced fewer shocks. This was not statistically significant compared to those not receiving statin therapy (27 patients [12.5%] vs. 7 patients [15.6%] p=0.60). There was also no difference in inappropriate shocks among those ICD patients treated with statins or those not treated with statins. In nonischemic cardiomyopathy, statins are associated with a reduction in mortality mostly due to a decrease in arrhythmic deaths. Because this was a substudy of a larger trial, these results should be confirmed in a prospective randomized trial to determine the benefits of statin therapy even in patients without hypercholesterolemia.

Mentzelopoulos SD, Zakyntinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009;169:15–24.

This single-center, prospective, double-blind, placebo-controlled, parallel-group trial randomized 100 patients requiring epinephrine for VT/VF, asystole or PEA to epinephrine 1 mg plus placebo (control group) or epinephrine 1 mg plus vasopressin 20 units (study group) for the first five cycles of CPR. Methylprednisolone 40 mg or placebo was administered during the first cycle of CPR to the study group and control groups, respectively. The primary end point was achievement of ROSC for ≥ 15 minutes and survival to hospital discharge. Patients in the study group had significantly higher rates of ROSC (vs. 52%; p=0.003) and were more likely to survive to hospital discharge (19% vs. 4%) when compared to the control group. Four hours post-resuscitation, 27 of 29 patients in the study group who had survived received stress-dose hydrocortisone (300 mg daily for 7 days with a

gradual taper) vs. 15 of 20 surviving patients in the control group who received placebo. Survival to hospital discharge occurred more frequently in the post-resuscitation shock patients in the study group as compared to similar patients in the control group (30% vs. 0%; p=0.02). More than 60% of patients presented with an initial rhythm of asystole, followed by PEA, then VT/VF. The higher rate of ROSC within 15 minutes was likely due to the combined epinephrine and vasopressin by increasing arterial pressure and improving coronary perfusion. The authors state that the combined drug treatment resulted in a 2.2-fold increase in the frequency of rapid resuscitation, decreasing the risk of death by 50%. Additionally, the use of hydrocortisone in the post-resuscitation period resulted in a 6.7-fold reduction in the risk of death.

Avezum A, Piegas LS, Goldberg RJ, et al. Magnitude and prognosis associated with ventricular arrhythmias in patients hospitalized with acute coronary syndromes (from the GRACE registry). *Am J Cardiol* 2008;102:1577–82.

This large, multinational nonrandomized observational study evaluated the incidence and outcomes associated with ventricular arrhythmias (VA) in patients admitted with an acute coronary syndrome. Additionally, patient characteristics associated with an increased risk for developing ventricular arrhythmias were identified. Using the Global Registry of Acute Coronary Events (GRACE) registry, 52,380 patients with acute coronary syndrome were evaluated. The overall frequency of ventricular arrhythmias was 6.9%, with 1.8% of these experiencing VT and 5.1% developing VF. Patients with ST-segment elevation MI were more likely to develop ventricular arrhythmias compared to those with non-ST segment elevation MI or unstable angina. Of those with an ACS that did develop ventricular arrhythmias, 55% did so on the first day of hospitalization. Age and female gender carried a higher risk for developing ventricular arrhythmias as well as a higher risk for dying during hospitalization compared to those patients who did not develop ventricular arrhythmias. Six-month mortality rates were higher in the VF group (12%) compared to the group without ventricular arrhythmias (5.1%) or the group who experienced VT only (6.5%). Patients with VF or VT are generally higher-risk patients than those without ventricular arrhythmias. A history of percutaneous coronary

intervention was associated with a decreased risk of developing ventricular arrhythmias.

Meaney PA, Nadkarni VM, Kern KB, et al. Rhythms and outcomes of adult in-hospital cardiac arrest. *Crit Care Med* 2010;38:101–8.

This study evaluated survival outcomes based on initial electrocardiographic rhythms in a cohort of patients experiencing cardiac arrest in a hospital setting. Data from 411 hospitals with 51,919 adults with cardiac arrest comes from AHA's National Registry of CPR which is a prospective, multisite resuscitation registry. The primary outcome was survival to hospital discharge with secondary outcomes including ROSC > 20 minutes, 24 hour survival and neurologic outcome. Asystole was the most frequent initial rhythm (39%), followed by PEA (37%), VF (17%) and pulseless VT (7%). Subsequent VT or VF occurred in approximately 25% of patients with an initial documented rhythm of asystole or PEA. Factors that related to the arrest were similar except patients first presenting with VT or VF predominantly experienced acute MI while hypotension or acute respiratory insufficiency were more associated with PEA and asystole. Additionally, patients presenting initially with a shockable rhythm were more likely to have preexisting cardiac disease, or a history of MI or HF. Survival to hospital discharge occurred in 51% of patients with VT/VF and 49% of patients with PEA/asystole. Additionally, 54% of VT/VF patients had favorable neurologic outcome compared to 46% of those with PEA/asystole. Outcomes were not different between VT or VF; however, PEA was slightly better than asystole in survival to discharge (12% vs. 11%; OR 1.09; 95% CI 1.00–1.18) and ROSC (45.2% vs. 39.6%; OR 1.14; 95% CI 1.08–1.12) but no differences in neurologic outcomes were noted. For patients with PEA/asystole who did not develop subsequent VT/VF, survival outcomes were better. There are limitations to this registry (such as data integrity, data validity and sampling bias); however, it provides useful epidemiologic, demographic, and outcome data in over 51,000 patients with cardiac arrest.

Dager WE, Sanoski CA, Wiggins BS, Tisdale JE. Pharmacotherapy considerations in advanced cardiac life support. *Pharmacotherapy* 2006;26:1703–29.

This review article describes the pharmacotherapeutic issues in ACLS and

summarizes major changes from the “2005 AHA guidelines for CPR and ECC.” This is an excellent resource for all health care professionals who participate as members of a cardiac arrest team. Topics covered include agents used for pulseless VT/VF, tachyarrhythmias, asystole, PEA, and symptomatic bradycardias. Some of the information covered includes mechanism of action, common adverse effects, and a brief review of the literature for each agent. Useful drug tables including dosing, class recommendations, and special considerations are provided. Additionally, the treatment of electrolyte abnormalities, hypotension, pulmonary embolism, and toxicology, as well as use of thrombolytic agents for ischemic stroke and acute MI is discussed. The authors describe the current information regarding the use of therapeutic hypothermia and briefly discuss the role of the pharmacist on cardiac arrest teams.

Drew BJ, Ackerman MJ, Funk M, Gibler WB, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 2010;121:1047–60.

This is the first scientific statement published on the prevention and treatment of torsade de pointes (TdP). This paper focuses on the patient in the hospital setting and briefly discusses the electrocardiographic characterizations of TdP, the cellular and genetic mechanisms of acquired long QT syndrome, risk factors and genetic susceptibility for long QT syndrome as well as drug-induced QT prolongation with or without TdP. A review of specific drugs and classes of drugs associated with TdP is included. For a more thorough review of the clinical relevance and management of drug-induced QT prolongation, the reader is referred to the paper by Crouch MA and associates in *Pharmacotherapy* 2003;23(7):881–908. This paper also discusses the differences in the ways to calculate and correct the QT interval and recommends a consistent method be used when monitoring patients before and after drug administration. A brief explanation of the treatment options for patients with TdP is included.

American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122(18 suppl3). Available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/.

The American Heart Association recently released their most updated guidelines for CPR and ECC (October 2010). The most significant change involved changing the sequence of steps for trained rescuers from A-B-C (airway, breathing and chest compression) to C-A-B for both adults and pediatric patients. This is to hopefully increase the number of bystanders willing to perform CPR. The compression rate has changed to at least 100/min instead of approximately 100 for adults. And the push down for adult breastbone should be at least 2 inches instead of 1.5–2 inches.

In terms of drug use in advanced cardiac life support, atropine is no longer recommended for routine use in the management of pulseless electrical activity (PEA)/asystole. This is because evidence suggests that routine use of atropine during PEA or asystole is unlikely to have therapeutic effect. Adenosine is now recommended for initial diagnosis and treatment of stable, undifferentiated, regular monomorphic wide complex tachycardia. In addition, post-cardiac arrest care now includes the recommendation of therapeutic hypothermia and percutaneous coronary intervention, when indicated, with more evidence of support for adults. Therapeutic hypothermia can also be considered for pediatric patients.

Chronic Management

Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA* 2005;293:2884–91.

In this double-blind, multicenter trial, 200 patients who were receiving an ICD for a recent episode of sustained VT or VF that was not due to an acute MI or a reversible cause (i.e., for secondary prevention) were randomized to receive fish oil 1.8 g/day (72% eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or placebo (olive oil). The primary end point was the time to first episode of VT/VF leading to ICD therapy (“shock”). At 6, 12, and 24 months, 46%, 51%, and 65% of patients in the fish oil group, respectively, had ICD therapy for VT/VF compared to 36%, 41%, and 59% of patients in the placebo group, respectively (p=NS). However, in a subgroup of 133 patients who received an ICD specifically for VT, significantly more patients in the fish oil group experienced ICD therapy for VT/VF compared to those who

received placebo. The incidence of recurrent VT/VF was also significantly increased in the patients who received fish oil when compared to placebo. Therefore, the results of this study suggest that fish oil may be proarrhythmic in patients who have received an ICD for secondary prevention of sudden cardiac death (SCD), especially in those individuals whose qualifying arrhythmia is sustained VT. Compliance was not assessed in this trial. The results of this trial were a bit unexpected given that fish oil supplementation has been previously associated with a significant reduction in SCD in several trials; however, these other trials enrolled patients who experienced a recent MI. Therefore, the conflicting results of all of these trials suggest that fish oil may exert its antiarrhythmic effects primarily in the setting of ischemically mediated VT/VF rather than under nonischemic conditions.

Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005;112:2762–8.

This study also evaluated the potential antiarrhythmic effects of fish oil in patients who had received an ICD for the secondary prevention of SCD. In this double-blind, multicenter trial, 402 patients with secondary prevention ICDs were randomized to receive fish oil 4 g/day (65% EPA and DHA) or placebo (olive oil) for 12 months. The primary end point was the time to first ICD event for VT/VF or death from any cause. The noncompliance rate was relatively high in this study (35%), but did not differ between the treatment groups. The mean time from ICD implantation to enrollment in the study was 1.6 years. In the intention-to-treat analysis, patients in the fish oil group experienced a 28% reduction in the primary end point when compared to those in the placebo group (95% CI 0.51–1.01; p=0.057). However, when a prespecified secondary analysis was performed to include only those patients (n=236) who were compliant with therapy for at least 11 months, patients in the fish oil group experienced a 38% reduction in the primary end point (95% CI 0.39–0.97; p=0.034). No significant differences in the primary end point were observed in various patient subgroups. Important limitations of this trial included its relatively high noncompliance rate and the difficulties experienced by the investigators in obtaining complete sets of electrocardiographic

data to document arrhythmic events.

Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* 2006;295:2613–9.

The Study on Omega-3 Fatty Acids and ventricular Arrhythmias is the largest prospective trial to evaluate the potential antiarrhythmic effects of fish oil in patients with ICDs. A total of 546 patients who had received an ICD because of a previous episode of VT or VF were randomized to receive either fish oil 2 g/day (40% EPA and DHA) or placebo (high-oleic acid sunflower oil). The primary end point was the incidence of appropriate ICD therapy (i.e., shock or anti-tachycardia pacing) for VT/VF or death from any cause. Patients were followed for a median of 356 days. Adherence was similar between the treatment groups, with nearly 80% of patients in both groups taking more than 80% of their assigned capsules. The primary end point occurred in 30% and 33% of patients in the fish oil and placebo groups, respectively (HR 0.86, 95% CI 0.64–1.16; $p=NS$). In addition, there was no significant difference in this end point between the treatment groups in those patients who had experienced VT in the previous 12 months or in those with a prior history of MI. Based on the results of this trial and those from the studies conducted by Raitt et al and Leaf et al, fish oil does not appear to have a protective effect against life-threatening ventricular arrhythmias in patients with ICDs. Therefore, the use of fish oil for the sole purpose of preventing ventricular arrhythmias in this specific patient population should not be recommended.

Connolly SJ, Dorian P, Roberts RS, et al. Comparison of β -blockers, amiodarone plus β -blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. *JAMA* 2006;295:165–71.

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial compared the efficacy of amiodarone, sotalol, and β -blockers for the prevention of ICD shocks in 412 patients who had received an ICD primarily for secondary prevention of SCD. Patients were randomized to receive β -blocker monotherapy (i.e., metoprolol, carvedilol, or bisoprolol), amiodarone plus a β -blocker (amiodarone 400

mg twice daily for 2 weeks, then 400 mg/day for 4 weeks, then 200 mg/day plus β -blocker from above), or sotalol (240 mg/day in 2–3 divided doses; dose adjusted for renal dysfunction). The primary end point was the first occurrence of any ICD shock. After 1 year, patients in the amiodarone plus β -blocker group experienced significantly fewer ICD shocks than patients in either the β -blocker (HR 0.27; 95% CI 0.14–0.52; $p<0.001$) or sotalol (HR 0.43; 95% CI 0.22–0.85; $p=0.02$) groups. Sotalol did not significantly reduce the risk of ICD shocks compared with the β -blocker group (HR 0.61; 95% CI 0.37–1.01; $p=0.055$). Patients in the amiodarone plus β -blocker group experienced significantly higher rates of pulmonary toxicity, hypothyroidism, and symptomatic bradycardia than the sotalol and β -blocker groups. The results of this trial should only be applied to a secondary prevention population, as patients who receive an ICD for primary prevention may be at lower risk for shocks due to ventricular arrhythmia. Although the results of this trial raise the question of whether concomitant AAD therapy should be initiated at the time of ICD implantation, the decision to start this therapy is usually made once the patient has been receiving frequent shocks. Based on the results of this trial, if AAD therapy is initiated in patients with a secondary prevention ICD, either amiodarone and a β -blocker or sotalol monotherapy would be a reasonable option.

Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.

While most of the previously conducted landmark primary prevention ICD trials limited enrollment to patients with ischemic cardiomyopathy, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) included both ischemic and nonischemic HF patients. This study is the largest primary prevention ICD trial to be conducted to date, enrolling 2521 patients with NYHA class II or III HF and a LVEF $\leq 35\%$. Patients were randomized to receive placebo, amiodarone, or a single-lead ICD. All patients were treated with appropriate HF therapies, as indicated. The primary end point was death from any cause. The median follow-up period was 45.5 months. A total of 52% of patients had ischemic HF, while 48% had nonischemic HF. Overall, the risk of death was significantly reduced in the ICD group when compared to

placebo (HR 0.77; 95% CI 0.62–0.96; $p=0.007$). There was no significant difference in the risk of death between the amiodarone and placebo groups (HR 1.06, 95% CI 0.86–1.30; $p=NS$). In a prespecified subgroup analysis, the survival benefits of the ICD were observed regardless of whether the HF was ischemic or nonischemic in etiology. Based on the results of this study, the indications for implanting ICDs have significantly expanded to include patients with NYHA class II or III HF.

Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:e247–346.

These guidelines provide a very useful overview of the epidemiology, pathophysiology, clinical presentation, and assessment of patients with ventricular arrhythmias. A detailed discussion of the various types of noninvasive tests (e.g., 12-lead electrocardiogram, exercise testing, ambulatory electrocardiogram, T-wave alternans, signal-averaged electrocardiogram, heart rate variability, echocardiography) and electrophysiological testing that can be employed to further evaluate patients with ventricular arrhythmias is included. Even though AADs have a limited role in the treatment of ventricular arrhythmias, these guidelines discuss the potential value of these agents in this setting and provide specific recommendations as to when these drugs may be appropriate to use in patients with or without an ICD. Various nonpharmacologic treatment modalities for ventricular arrhythmias, including ICDs, automated external defibrillators, and surgical or revascularization procedures are also discussed. Detailed recommendations for reducing the risk of SCD in specific patient populations including those with ischemic, nonischemic, or hypertrophic cardiomyopathies, metabolic or inflammatory conditions, long QT syndrome, Brugada syndrome, or structurally normal hearts are also included in these guidelines. Recommendations for managing drug-induced toxicities that may lead to the development of ventricular

arrhythmias including digoxin toxicity, drug-induced long QT syndrome, and sodium channel blocker toxicity are also discussed.

Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;4:1250–9.

These guidelines serve as an update to those published in 2000. A useful background regarding the role of oral and IV amiodarone for the treatment of various atrial and ventricular arrhythmias is provided. The most valuable section of this updated guide is that which contains the recommendations regarding the appropriate monitoring of amiodarone therapy. Specifically, recommendations for monitoring chest x-rays, liver function tests, thyroid function tests, ophthalmologic exams, pulmonary function tests, and 12-lead electrocardiograms are outlined. The table that contains an overview of the incidence, diagnosis, and management of amiodarone's various organ toxicities is particularly informative. A more detailed discussion of amiodarone-induced pulmonary and thyroid dysfunction, including clinical and laboratory test manifestations, diagnostic criteria, treatment recommendations, and advice for when a specialist (i.e., pulmonologist or endocrinologist) should be consulted is also included in these guidelines. This updated guide also outlines the specific information that should be obtained from the history and physical exam of a patient who is receiving chronic amiodarone therapy.

Ferreira-González I, Dos-Subirá L, Guyatt GH. Adjunctive antiarrhythmic drug therapy in patients with implantable cardioverter defibrillators: a systematic review. *Eur Heart J* 2007;28:469–77

This systematic review assesses the efficacy and safety of various adjunctive AADs for reducing the incidence of ICD therapies ("shocks"). To be included in this systematic review, trials had to meet the following criteria: 1) possessed a randomized, controlled, parallel study design; 2) enrolled patients with an ICD for the primary or secondary prevention of SCD; 3) used AADs as the intervention; 4) used placebo or β -blockers as the control; 5) followed-up patients for at least 12 months; and 6) prespecified at least one of the end points in the study protocol. The primary efficacy outcome of this systematic review was the risk of the first ICD therapy. Safety outcomes

included discontinuation of therapy for any reason and new or worsening HF. A total of eight trials, involving 1889 patients, met the inclusion criteria and were included in the analysis. The results of this systematic review revealed that the risk of the primary efficacy outcome was significantly reduced with concomitant amiodarone and β -blocker therapy when compared to β -blocker monotherapy (HR 0.27; 95% CI 0.14–0.52) and with sotalol when compared to placebo (HR 0.55; 95% CI 0.40–0.78). The risk of the primary efficacy outcome did not significantly differ when sotalol was compared to β -blocker therapy and when dofetilide and azimilide were compared with placebo. The risk for discontinuing therapy was significantly higher in patients treated with class III AADs than in those who received β -blocker therapy. The risk of new or worsening HF also tended to be higher in patients receiving class III AADs than in those receiving β -blockers. Limitations of this analysis include the relatively small number of included studies, differences in quality across the studies, and heterogeneity of end points evaluated in the included studies.

Packer DL, Prutkin JM, Hellkamp AS, et al. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the Sudden Cardiac Death in Heart Failure. *Circulation* 2009;120:2170–6.

This follow-up analysis evaluated the specific causes of death in the SCD-HeFT. In his landmark trial, a total of 666 deaths (22% ICD, 28.4% amiodarone, 28.8% placebo) occurred over a median follow-up period of 45.5 months and were initially characterized as being either cardiac or noncardiac in nature. Cardiac mortality occurred in 14.7%, 19.2%, and 19.7% of patients who received an ICD, amiodarone, and placebo, respectively. When compared to placebo, patients in the ICD group experienced a 24% reduction in cardiac mortality ($p=0.018$). However, no significant difference in this end point was observed between the amiodarone and placebo groups. Upon further evaluation of these cardiac deaths, patients in the ICD group experienced a 60% reduction in death due to tachyarrhythmia (presumed to be ventricular in nature) when compared to placebo ($p<0.001$). This reduction in tachyarrhythmia mortality occurred regardless of whether the patients had ischemic or nonischemic HF. No significant difference occurred with regard to death due to

tachyarrhythmia between the amiodarone and placebo groups. Cardiac mortality due to HF did not significantly differ between the treatment groups. When the mode of death was analyzed by NYHA class, ICD therapy significantly reduced cardiac mortality and mortality due to tachyarrhythmia by 50% and 74%, respectively, in patients with NYHA class II HF. However, ICD therapy had no significant effect on any cause of death in those with NYHA class III HF. Further analysis of the patients with NYHA class III HF revealed that the lack of benefit with ICD therapy was only observed in those patients (10%) who were at highest risk for mortality; the remainder of the group did experience a reduction in sudden death with ICD therapy. Therefore, the results of this subgroup analysis may have been skewed by this high-risk population, and should be interpreted with caution.

Mark DB, Anstrom KJ, Sun JL, et al. Quality of life with defibrillator therapy or amiodarone in heart failure. *N Engl J Med* 2008;359:999–1008.

Even though a number of trials have established that the ICD is significantly more effective than AAD therapy in improving survival in patients who are at high-risk for SCD (“primary prevention”), there has been some concern about the effect that these devices may have on patient QOL. This analysis from the SCD-HeFT evaluated the impact of ICD therapy on health-related QOL. The psychological well-being of patients was significantly better in the ICD group than in the placebo group at 3 and 12 months; however, there was no difference in this outcome at 30 months. No significant difference was observed with regard to physical functioning between the ICD and placebo groups at any of the time points. There were no significant differences between the amiodarone and placebo groups in any of the QOL measures. In the subgroup of patients in the ICD group who experienced a shock within one month before a QOL assessment, a significant decline in QOL in a variety of categories was observed. However, these results should be cautiously interpreted due to the relatively small number of patients who received a shock prior to their assessment. Therefore, during a period of 30 months, the use of ICDs for the primary prevention of SCD significantly improved survival without having any deleterious effects on health-related QOL.

Hohnloser SH, Dorian P, Roberts R, et al. Effect of amiodarone and sotalol on ventricular defibrillation threshold: the Optimal

Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial. *Circulation* 2006;114:104–9.

This substudy of OPTIC aimed to prospectively assess the effects of amiodarone and sotalol on defibrillation energy requirements in patients with an ICD, which is usually measured as the defibrillation threshold (DFT). A total of 94 patients from the OPTIC trial underwent DFT testing at baseline and then at 8 to 12 weeks after therapy was initiated. In this cohort, 29 patients received β -blocker therapy, 35 received concomitant amiodarone and β -blocker therapy, and 30 received sotalol. The mean change in DFT was the primary end point of this analysis. When compared to baseline, the mean DFT significantly decreased by 1.64 J in the β -blocker group ($p=0.027$). The mean DFT increased by 1.29 J in the amiodarone/ β -blocker group and decreased by 0.89 J in the sotalol group, neither of which were significant changes from baseline. When comparisons were performed between the treatment groups, significant differences in the mean change in DFT were observed between the β -blocker and amiodarone/ β -blocker group and the sotalol and amiodarone/ β -blocker group. Only one patient (who received concomitant amiodarone and β -blocker therapy) had a DFT increase of more than 10 J. There was no patient characteristic that independently predicted the changes in DFT from baseline in any of the treatment groups. The authors acknowledged that a 1-J mean increase in required defibrillation energy is unlikely to have a significant impact on outcomes. Therefore, although the change in DFT from baseline in the amiodarone/ β -blocker group was considered to be statistically significant, it was not deemed to be clinically relevant. Overall, based on the results from the amiodarone and sotalol groups, routine DFT reassessment after initiation of these AADs in patients with an ICD does not appear to be warranted.

Brodine WN, Tung RT, Lee JK, et al. Effects of β -blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the Multicenter Automatic Defibrillator Implantation Trial-II). *Am J Cardiol* 2005;96:691-5.

In the previously conducted Multicenter Automatic Defibrillator Implantation Trial-II, patients with a prior MI and an LVEF $\leq 30\%$ who had received an ICD experienced a significant reduction in mortality. A post-hoc analysis of

data from this trial was performed in 691 patients (433 received β -blocker therapy) who received ICDs to assess the effects of β -blocker therapy on the incidence of appropriate ICD therapy for VT/VF, inappropriate ICD therapy for supraventricular arrhythmias, and overall survival. Patients receiving the most common β -blockers, including carvedilol, metoprolol, and atenolol, were included in this analysis. Patients who received β -blocker therapy were divided into the upper quartile (“larger dose”) and lower three quartiles (“small dose”) of the β -blocker doses they were taking. Appropriate ICD therapy for VT/VF was significantly reduced in the patients receiving the larger dose of β -blockers when compared to those not receiving β -blocker therapy. However, there was no significant difference in the incidence of inappropriate ICD therapy for supraventricular arrhythmias between the treatment groups (no β -blocker, small-dose β -blocker, larger-dose β -blocker). Use of either small-dose or larger-dose β -blocker therapy was associated with a significant reduction in mortality when compared to no β -blocker therapy. This analysis is limited by its post-hoc design and the lack of standardization for initiating β -blocker therapy (decision regarding selection of drug and dose left up to patient’s physician). Nevertheless, the results of this analysis do suggest that the use and titration of β -blocker therapy in patients with a history of MI and LV systolic dysfunction who have ICD would be associated with antiarrhythmic and survival benefits.

Piccini JP, Berger JS, O’Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009;30:1245–53.

This updated meta-analysis evaluated the efficacy and safety of amiodarone for the prevention of SCD. Studies that randomized patients to receive amiodarone, placebo, or inactive control, involved a treatment duration of more than 30 days and a follow-up period of at least 6 months, and evaluated all-cause mortality as an end point were included in this analysis. Studies involving ICDs were excluded from the analysis unless patients in the treatment and control groups had received an ICD. A total of 15 trials that randomized 8522 patients to receive amiodarone or placebo/control were included in this analysis. All of the included studies (with the exception of OPTIC) were primary prevention trials and enrolled patients with a mean LVEF

that ranged from 18–44%. The use of amiodarone was associated with significant reductions in SCD (OR 0.72; 95% CI 0.61–0.84; $p < 0.001$) and CV mortality (OR 0.82; 95% CI 0.71–0.94; $p = 0.004$) when compared to placebo/control. However, there was no significant difference in all-cause mortality or death due to HF between the groups. The incidence of pulmonary, thyroid, and hepatic toxicities and bradyarrhythmias was significantly higher in the amiodarone group than in the placebo/control group. The rate of drug discontinuation was also significantly higher in the amiodarone group than in the placebo group. Even though the results of previous retrospective analyses have associated amiodarone with an increase in all-cause mortality, the results of this meta-analysis suggest that amiodarone does not have a detrimental effect on survival. Although ICDs have essentially supplanted the use of AAD therapy for the primary prevention of SCD, the results of this analysis suggest that amiodarone therapy may be a viable option for patients who are at high risk for SCD and are not eligible for ICD placement.

Kamath GS, Mittal S. The role of antiarrhythmic drug therapy for the prevention of sudden cardiac death. *Prog Cardiovasc Dis* 2008;50:439–48.

Numerous trials have established that the ICD is significantly more effective than AAD therapy in improving survival in both primary and secondary prevention patient populations. However, AAD therapy may still have a role in patients who have received an ICD to decrease the frequency of appropriate shocks from VT/VF or to manage episodes of concomitant supraventricular arrhythmias (including AF) that could trigger inappropriate shocks. This review article discusses the role of various AADs for the secondary and primary prevention of SCD. Specifically in the primary prevention population, the discussion is focused on the role of these agents in patients who are at high risk for SCD because of a history of MI or LV systolic dysfunction. A review of trials that have evaluated the efficacy of the concomitant use of AADs in patients with ICDs is also included.

Majmudar MD, Tompkins C, Bachmann JM, Blumenthal RS, Marine JE. Effects of lipid-altering therapies on ventricular arrhythmias and sudden cardiac death. *Cardiol Rev* 2009;17:60–9.

While statin therapy has an established role in

the primary and secondary prevention of various forms of CV disease, there has been increasing evidence that these drugs may also have antiarrhythmic properties. Considerable research has been devoted to evaluating the antiarrhythmic properties of these agents and their potential role in the prevention and treatment of supraventricular and ventricular arrhythmias. This review article specifically focuses on the effects of statins and polyunsaturated fatty acids (“fish oils”) on ventricular arrhythmias and SCD. The potential antiarrhythmic mechanisms of both of these classes of drugs are discussed. The pertinent details of the trials that evaluated the efficacy of statins and polyunsaturated fatty acids for the prevention of VT/VF and SCD are included; however, most of this discussion is focused on the latter category of drugs because of the clinical evidence that has accumulated in this area. Data regarding the effects of these drugs on the incidence of appropriate ICD therapy for VT/VF are also discussed.

Dopp AL, Miller JM, Tisdale JE. Effect of drugs on defibrillation capacity. *Drugs* 2008;68:607–30.

One of the concerns of using concomitant AADs in patients with an ICD is that these agents may alter the device’s DFT and subsequently affect its overall function. This article provides a comprehensive, evidence-based review of the effects of various drugs, including the class I and III antiarrhythmics, β -blockers, verapamil, digoxin, venlafaxine, and anesthetic agents, on the defibrillation capacity of ICDs. This review also provides a helpful overview of not only the methods that are used in measuring the DFT in patients with ICDs but also the various mechanism by which drugs can affect defibrillation capacity. In the section that focuses on the effects of specific drugs on the defibrillation capacity, the evidence for each drug is presented in an organized fashion, with the results of animal studies, case reports, and human studies being discussed. A table is also included in this review article that provides a useful summary of whether these drug increase, decrease or have no effect on DFT.

Non-Pharmacologic Management

Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy for cardiac rhythm abnormalities. *Circulation* 2008;117:e350–e408.

This is an evidence based guideline developed by ACC, AHA and HRS providing clinicians recommendations on appropriate use of CV devices [including pacemakers, cardiac resynchronization therapy (CRT) and ICDs]. Standard AHA/ACC classifications and recommendations system are used. Clinical pharmacists working with patients with CV diseases will encounter the use of many of these devices in practice. It is important to develop a basic understanding of their appropriate clinical indications. The following summarizes the major Class I indications for different devices.

Permanent pacemaker implantation is indicated for sinus node dysfunction with documented symptomatic bradycardia, as well as chronotropic incompetence. It is also indicated for symptomatic sinus bradycardia that results from required drug therapy for other medical conditions (e.g., β -blockers, non-dihydropyridine CCBs and digoxin). Permanent pacemakers are also recommended to be used in patients with advanced second-degree AV nodal block, type II second degree AV block or third-degree heart block (intermittent or persistent). It is also indicated for recurrent syncope caused by spontaneous carotid sinus stimulation, as well as for sustained pause-dependent VT with or without QT interval prolongation.

Cardiac resynchronization therapy is indicated for patients who have an LVEF \leq 35%, QRS duration \geq 0.12 seconds, and SR. Cardiac resynchronization therapy with or without an ICD is indicated for improvement of symptoms in patients who have NYHA Class III or IV HF.

An ICD is indicated in patients who are cardiac arrest survivors due to VF or hemodynamically unstable sustained VT, those who have structural heart disease and spontaneous sustained VT, and those who have syncope of unknown origin and inducible VT or VF on electrophysiological study. An ICD is also indicated in patients with an LVEF \leq 35% due to an MI (at least 40 days post-MI), or nonischemic dilated cardiomyopathy, and are in NYHA functional Class II or III. In patients with nonsustained VT due to prior MI and LVEF \leq 40%, an ICD is also indicated if they have inducible VT or VF during an electrophysiological study.

Stevenson WG, Chaitman BR, Ellenbogen KA, et al. Clinical assessment and management of patients with implanted cardioverter-defibrillators presenting to nonelectrophysiologists. *Circulation* 2004;110:3866–9.

Clinical pharmacists working in any areas will increasingly encounter patients who have ICDs for prevention of life-threatening ventricular arrhythmia. This advisory provides a concise summary, written in language for non-electrophysiologists, of information relevant to the assessment and management of patients with ICDs, including those who present to primary care or the emergency department with symptoms suggesting of arrhythmia or ICD malfunction and those who require cardiac or other surgical procedures. From a pharmacy practice point of view, the important take-home message is when to appropriately direct patients who report symptoms of being shocked by the ICD for emergent evaluation. The advisory recommends that patients who report an isolated shock with no symptoms to suggest a change in health status should otherwise be reassured and do not require emergent evaluation, especially if they have had such events previously separated by long periods of stability. However, these patients should be advised to follow-up with their electrophysiologists shortly thereafter. Patients who experience a shock and feel unwell after the event or who receive more than one symptomatic ICD shock within a short period of time (minutes to hours) should be directed for emergent evaluation.

Priori SG, Bossaert LL, Chamberlain DA, et al. ESC-ERC recommendations for the use of automated external defibrillators (AEDs) in Europe. *Eur Heart J* 2004;25:437–45.

The training of the public in the use of AEDs has been demonstrated to save lives (the AHA notes that at least 20,000 lives could be saved annually by prompt use of AEDs). Any health care professional including pharmacists should be encouraged to get familiar with the use of AEDs in order to assist patients should the situation arise. This guideline developed by the European Society of Cardiology and the European Resuscitation Council made recommendations for legislation on the use of defibrillation, for AED training and for the development of AED community programs in order to make AEDs accessible to the public.

Kuck KH, Schaumann A, Eckardt L, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomized controlled trial. *Lancet*. 2010;375:31–40.

In patients with VT and a history of MI, the use of ICDs has been demonstrated to prevent SCD. However, if patient have a high VT burden, frequent ICD shocks are painful and significantly impact patients' QOL. Treatment with AADs and/or catheter ablation, are two strategies to reduce the number of ICD shocks. The VTACH study was a prospective, open-labeled, randomized controlled trial, designed to evaluate the potential benefit of catheter ablation before implantation of an ICD. The primary end point was the time to first recurrence of VT or VF. A total of 117 patients were included in the analysis (ablation group, n=52; control group, n=55). Time to recurrence of VT or VF was longer in the ablation group (median 18.6 months) than in the control group (5.9 months). At 2 years, estimates for survival free from VT or VF were 47% in the ablation group and 29% in the control group (HR 0.61; 95% CI 0.37–0.99; p=0.045). Complications related to the ablation procedure occurred in two patients (transient ST-segment elevation and transient cerebral ischemia). Five patients in the ablation group and four patients in the control group died during the study. The results of this study suggest that catheter ablation is an effective strategy in delaying recurrent VT/VF and reducing ICD shocks. However, this study was limited by its relatively small sample size and the low rate of ablation complications. The latter might be due to the fact that the study was performed in centers with experienced clinicians. The study also did not evaluate whether the additional costs of catheter ablation would be compensated by the reduced number of hospital admissions in patients with ICD. This study also did not compare ablation with treatment using AADs. Therefore, comment can be made regarding the relative efficacy of these two therapeutic strategies in this setting.

Knecht S, Sacher F, Wright M, et al. Long-term follow-up of idiopathic ventricular fibrillation ablation: a multicenter study. *J Am Coll Cardiol* 2009;54:522–8.

The gold standard treatment for either primary or secondary prevention of VF is the placement of an ICD. However, although ICD can be life-saving at the time of an event, it does not prevent the event from occurring. Previous experimental and clinical studies have demonstrated the importance of the Purkinje network in the initiation of VF. Catheter ablation of idiopathic VF that targets VPB triggers from the Purkinje network has been shown to prevent VF

recurrences on short-term follow-up. However, the long-term outcomes of patients after VF ablation has been unknown. This study was designed to evaluate the long-term effect of targeted ablation of triggering VPBs in patients with VF. Thirty-eight patients who underwent ablation for idiopathic VF initiated by short-coupled VPBs were included in this follow-up. Median post-procedural follow-up duration was 63 months. During the follow-up period, 7 (18%) of the patients experienced VF recurrence at a median of 4 months. Five of these particular patients underwent repeat ablation without VF recurrence. The number of significant events (confirmed VF or aborted sudden death) was reduced from 4 before to 0 after ablation (p=0.01). Important limitations of the study included that this was an observational study with no control group. Ventricular fibrillation is a sporadic event and it is difficult to conclude with certainty that the absence of VF recurrence in this study was due to the success of the ablation or due to chance. In addition, patients were allowed to receive AAD therapy. Therefore, it is impossible to exclude the impact of additional AADs in suppressing the arrhythmias. Ablation of idiopathic VF appears to result in excellent long-term outcomes. However, without confirmation from larger scale study with control group, ablation therapy does not replace ICD for prevention of SCD.

Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009;361:1427–36.

Sudden cardiac death due to VT accounts for approximately 20–50% of all deaths in post-MI patients. With the exception of β -blockers, AADs do not reduce such risk. Randomized studies have shown that an ICD can reduce mortality both among patients who have had sustained VT and among selected patients who have a depressed LVEF without ventricular arrhythmias. However, guidelines based on the results of these trials recommend that implantation of an ICD for the primary prevention of SCD should be withheld for at least 40 days after an acute MI. The Immediate Risk Stratification Improves Survival (IRIS) trial was a randomized, prospective, open-label, multicenter trial enrolling 898 patients 5–31 days after a MI, to compare ICD, if placed within the first 30 days after MI versus medical therapy alone in reducing SCD. During a mean follow-up of 37 months, 233 patients died (116 patients in the ICD group

and 117 patients in the control group). Overall mortality was not reduced in the ICD group (HR, 1.04; 95% CI 0.81–1.35; $p=0.78$). There were fewer SCDs in the ICD group than in the control group (HR, 0.55; 95% CI 0.31–1.00; $p=0.049$), but the number of non-SCDs was higher in the ICD group (HR, 1.92; 95% CI 1.29–2.84; $p=0.001$). The investigators concluded that prophylactic ICD therapy within the first 30 days after an MI did not reduce overall mortality.

Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;359:1009–17.

Patients with HF who receive an ICD for primary prevention may later receive therapeutic shocks from the ICD. Information about long-term prognosis after ICD therapy for primary prevention of SCD is limited in patients with HF. This was a subanalysis of the SCD-HeFT database designed to evaluate the long-term prognostic significance of both appropriate and inappropriate ICD shocks. The SCD-HeFT was a multicenter clinical trial in which 2521 patients with NYHA class II or III HF and a LVEF $\leq 35\%$, but no previous sustained ventricular arrhythmia, were randomly assigned to receive an ICD, amiodarone therapy, or placebo. After a median follow-up of 45.5 months, ICD therapy, as compared with amiodarone alone, was associated with a 23% reduction in the risk of death. A total of 269 patients (33.2%) received at least one ICD shock, with 128 patients receiving only appropriate shocks, 87 receiving only inappropriate shocks, and 54 receiving both types of shock. In a Cox proportional-hazards model adjusted for baseline prognostic factors, an appropriate ICD shock, as compared with no appropriate shock, was associated with a significant increase in the subsequent risk of death from all causes (HR, 5.68; 95% CI 3.97–8.12; $p<0.001$). For patients who survived longer than 24 hours after an appropriate ICD shock, the risk of death remained elevated (HR, 2.99; 95% CI 2.04–4.37; $p<0.001$). The most common cause of death among patients who received any ICD shock was progressive HF. This study indicated that appropriate defibrillator shocks have prognostic importance in patients with HF. However, it is important to note that primarily single-lead ICDs were used in the SCD-HeFT, and shocks were programmed for high-rate arrhythmias that were most likely to be life-threatening.

Bardy GH, Lee KL, Mark DB, et al. Home use of automated external defibrillators for sudden cardiac arrest. *N Engl J Med* 2008;358:1793–804.

Out-of-hospital sudden cardiac arrest takes place commonly at home, a situation in which emergency medical services are challenged to provide timely care. Therefore, home use of an AED might improve survival for patients at risk. This study was designed to evaluate the effectiveness of AEDs in saving lives in an out-of-hospital setting. A total of 7001 patients with previous anterior-wall MI who were not candidates for an ICD were randomized to receive one of two responses to sudden cardiac arrest occurring at home: control response (calling emergency medical services and performing CPR) or the use of an AED, followed by calling emergency medical services and performing CPR. The primary outcome was death from any cause. The median follow-up was 37.3 months. Overall, 450 patients died (228 of 3506 patients [6.5%] in the control group and 222 of 3495 patients [6.4%] in the AED group) (HR, 0.97; 95% CI 0.81–1.17; $p=0.77$). However, only 160 deaths (35.6%) were considered to be from sudden cardiac arrest from tachyarrhythmia. Of these deaths, 117 occurred at home and only 58 at-home events were witnessed. Automated external defibrillators were used in only 32 patients. Of these patients, 14 received an appropriate shock, and 4 survived to hospital discharge. There were no documented inappropriate shocks. The investigators concluded that, for survivors of anterior-wall MI who were not candidates for implantation of an ICD, access to a home AED did not significantly improve overall survival as compared with conventional resuscitation methods. However, it is important to note that only 50% of the events were witnessed and even in the witness event, only approximately half of those who were randomized to AED actually utilized the therapy. Therefore, a better system in training the lay public and using AEDs effectively may improve the outcome. It is also important to recognize that this result may not apply to the use of AEDs in higher-risk populations. Candidates who required an ICD were excluded from this study. It is possible that a population with a higher event rate and a greater proportion of sudden deaths from tachyarrhythmia might benefit from access to a home AED.

Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention

of defibrillator therapy. *N Engl J Med* 2007;357:2657–65.

In patients with VT, ICDs have been demonstrated to prevent SCD and reduce mortality. However, if patients have a high VT burden, frequent ICD shocks are painful and significantly impact QOL. This study was designed to examine whether prophylactic radiofrequency catheter ablation of arrhythmogenic ventricular tissue would reduce the incidence of ICD shocks. A total of 128 eligible patients with a history of an MI and spontaneous VT or VF underwent ICD placement. The patients did not receive AADs. Patients were randomly assigned to ICD implantation alone or ICD implantation with adjunctive catheter ablation (64 patients in each group). The primary end point was survival free from any appropriate ICD shock. The mortality rate 30 days after ablation was zero, and there were no significant changes in ventricular function or functional class during the mean follow-up period of 22.5 months. Twenty-one patients assigned to ICD implantation alone (33%) and eight patients assigned to ICD implantation plus ablation (12%) received appropriate ICD therapy (anti-tachycardia pacing or shocks) (HR 0.35; 95% CI 0.15–0.78; $p=0.007$). There was no difference observed in mortality in the ablation plus ICD versus the ICD alone group (9% vs. 17%; $p=0.29$). This study was limited by the small number of participants. In addition, during enrollment, screening data were not collected; this may limit our understanding of how to select the most appropriate patients for ablation and how to generalize the data to other patients. Finally, this study did not compare ablation with AAD therapy, and therefore we cannot comment directly on the relative efficacy of these two therapeutic approaches in this setting.

Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351:2481–8.

Implantable cardioverter-defibrillator therapy has been shown to improve survival in patients with various heart conditions who are at high risk for ventricular arrhythmias. Before this study was performed, whether benefit occurred in patients early post-MI was unknown. This randomized, open-label study was designed to compare ICD ($n=332$) versus no-ICD ($n=342$) in patients 6–40 days after an MI with an LVEF \leq

35%. During a mean follow-up period of 30 months, there was no difference in overall mortality between the two treatment groups (HR 1.08; 95% CI 0.76–1.55; $p=0.66$). There were 12 deaths due to arrhythmia in the ICD group, as compared with 29 in the control group (HR 0.42; 95% CI 0.22–0.83; $p=0.009$). In contrast, there were 50 deaths from nonarrhythmic causes in the ICD group and 29 in the control group (HR 1.75; 95% CI 1.11–2.76; $p=0.02$). The reason for the unexpected increase in mortality from causes other than arrhythmia in patients assigned to receive an ICD is not clear. The most likely explanation is that the patients “saved” from an arrhythmia-related death by ICD therapy are also at high risk for death from other cardiac causes. Use of amiodarone was more common in the control group than it was in the ICD group. Most likely, this particular difference is a reflection of physicians’ desire in this unblinded study to provide additional optimal therapy in the absence of an ICD. It is not clear if amiodarone had any effect on survival observed in this trial.

Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med*. 2004;350:2151–8.

Patients with nonischemic dilated cardiomyopathy are at substantial risk for SCD. However, the value of prophylactic implantation of an ICD to prevent SCD in such patients was unknown prior to the publication of this study (also known as the DEFINITE trial). This was a randomized study comparing ICD implantation ($n=229$) versus standard medical therapy ($n=229$) in patients with nonischemic dilated cardiomyopathy (LVEF $\leq 35\%$) and premature ventricular complexes or nonsustained VT. Patients were followed for a mean of 29 months. There were 28 deaths in the ICD group as compared with 40 in the standard-therapy group (HR, 0.65; 95% CI 0.40–1.06; $p=0.08$). The mortality rate at 2 years was 14.1% in the standard-therapy group and 7.9% in the ICD group. There were 3 sudden deaths from arrhythmia in the ICD group, as compared with 14 in the standard-therapy group (HR, 0.20; 95% CI 0.06–0.71; $p=0.006$). On the basis of the results, the routine implantation of an ICD cannot be recommended for all patients with nonischemic cardiomyopathy and low LVEF. However, the reduction in sudden death from arrhythmia and an apparent benefit of ICDs in subgroup analyses suggest that the use of these

devices should be considered on a case-by-case basis. This study did not include a group of patients who were treated with amiodarone.

Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140–50.

Short-term studies have demonstrated that CRT improved symptoms and QOL, and increased exercise tolerance in patients with Class III HF. An ICD can reduce the risk of death among patients who have ischemic cardiomyopathy and no history of sustained ventricular arrhythmia but it is not clear whether such prophylactic therapy would be beneficial in patients who have advanced with severe LV dysfunction or in those with nonischemic cardiomyopathies. In this study, also known as the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, a total of 1520 patients who had advanced HF (NYHA class III or IV) due to ischemic or nonischemic cardiomyopathies and a QRS interval ≥ 120 msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy (diuretics, ACE inhibitors, β -blockers, and spironolactone) alone or in combination with CRT with either a pacemaker or a pacemaker-defibrillator. The primary composite end point was the time to death from or hospitalization for any cause. As compared with optimal pharmacologic therapy alone, CRT with a pacemaker decreased the risk of the primary end point (HR, 0.81; $p=0.014$), as did CRT with a pacemaker-defibrillator (HR, 0.80; $p=0.01$). The risk of the combined end point of death from or hospitalization for HF was reduced by 34% in the pacemaker group ($p<0.002$) and by 40% in the pacemaker-defibrillator group ($p<0.001$ for the comparison with the pharmacologic therapy group). Data from this study indicate that, in a population with advanced HF and an increased QRS interval, adding a defibrillator to CRT significantly reduces the risk of death and hospitalization.

Lim HS, Singleton CB, Alasady M, et al. Catheter ablation for ventricular tachycardia. *Intern Med J* 2010;40(10):673–81.

Recent advances in catheter ablation for VT have increased the efficacy by creating adequate lesions, accurate 3-dimensional maps, and mapping hemodynamically unstable VT. This

has led to the increased utility of this modality in the treatment of ventricular arrhythmias. This is a review article discussing the evolution of, recent advances and clinical utility of VT ablation. It is written for non-electrophysiologists making it easy to understand for clinical pharmacists practicing in any setting.

Pedersen SS, van den Broek KC, Sears SF Jr. Psychological intervention following implantation of an implantable defibrillator: a review and future recommendations. *Pacing and Clin Electrophysiol* 2007;30:1546–54.

The superiority of the ICD compared to AADs for the prevention of SCD both in primary and secondary prevention is well established. Nevertheless, a subgroup of patients with ICDs experiences emotional difficulties (24–87%), with symptoms of anxiety and depression. For this subgroup, some form of psychological intervention may be warranted. This review provides an overview of current evidence on the efficacy of psychological intervention in ICD patients and recommendations for future research. Most interventions were multifactorial, using cognitive behavioral therapy as one of the mainstays of treatment. Some studies found a reduction in depressive symptoms and improvements in QOL, but the most notable effects were seen in improved exercise capacity and reductions in anxiety. Preliminary evidence from small-scale intervention trials suggests that psychological intervention is worthwhile in ICD patients. However, large-scale, well-designed trials are warranted to substantiate these findings. A multifactorial approach using a cognitive behavioral component paired with exercise training appeared to be the most successful.

Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. *JAMA* 2006;295:809–18.

Implantable cardioverter-defibrillators have been shown to improve survival as both primary and secondary prophylaxis in an expanding population of patients. Since its introduction, there have been numerous advances in ICD technology, and indications for the use of ICDs have expanded greatly in the past year. This is an article reviewing the evolving indications of ICD and the advances in ICD technology. Implantation of an ICD improves survival in patients with a history of life-threatening ventricular arrhythmia. More recent evidence

shows that ICD implantation also improves survival as primary prophylaxis against SCD in patients at high risk for ventricular arrhythmias, including those with an LVEF $\leq 35\%$ and NYHA class II or III HF and those with a history of MI

and LVEF $\leq 30\%$. Ongoing ICD research may continue to delineate groups with survival benefit from ICDs, and the use and indications of these devices in clinical practice will continue to expand.