THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

NUMBER 134 **October/November 2014** **14th YEAR**

Welcome to the Oct/Nov issue of The AFIB Report in which we return to our more traditional format, taking a summary look at some of the more relevant AFIB-related studies published in recent months addressing topics of interest for both the lay 'afibber' and health professional alike, and offering practical real-world guidelines.

Our prime focus in this issue is a collection of subjects garnering increasing investigative effort in the last few years, centered on life-style issues that can negatively impact the course of AFIB, and modification of which can make a positive long-term contribution toward minimizing our total AFIB burden over time. Indeed, the very same core focus of the past 14 years here at the heart of this newsletter and associated website: http://www.afibbers.org.

First at bat, we look at one of the top avoidable triggers for many afibbers – excessive alcohol consumption. We all are well aware of the association, but now we have some hard data on a dose/response relationship to help guide a reasonable approach to alcohol intake, such as when alcohol might be used in moderation and when best to leave it alone. Also, key insights into types of alcoholic drinks and their relative influence as triggers are discussed.

Next we review two very informative large Scandinavian studies on the role of endurance exercise and it's association with AFIB. Again, a topic we have visited in the recent past, but with new insights here into a long-term dose/response relationship between low to moderate and moderate to intensive endurance exercise and AFIB over time, including the influence of age.

Exciting news as well from the NOAC (novel oral anticoagulant) arena, with a just off the press trial using Xarelto (rivaroxaban) in place of warfarin for elective cardioversion that offers the prospect of greatly shortening the time to early cardioversion, while improving both outcome and safety.

Another breaking NOAC-related news item reveals positive results from a phase-3 study on the new NOAC Factor Xa inhibitor antidote, ***Andexanet Alfa,*** *by Portola Pharmaceuticals that is very much worth hearing about.*

Back at the dawn of The AFIB Report, and long before the majority of cardiologists and EPs were aware of the problem, founder Hans Larsen alerted us all to the dangers of digoxin use as a rate control drug for treating AFIB. Now we see full confirmation and vindication of Hans' pioneering insights on this key issue from the TREAT-AF study, showing that digoxin use is significantly associated with increased risk of death, even in patients with newly diagnosed AFIB.

Finally, a new study out of the respected EP group at Intermountain Heart Institute in Utah gives compelling evidence of a significantly lower long-term stroke risk in AFIB ablation patients compared to AFIB patients who do not undergo ablation across all age strata, and independent of baseline CHADS2 risk score. In fact, stroke risks for those completing a successful ablation process are on par with that for the same age group population who has never had AFIB. Reassuring findings, indeed!

Wishing you all good health and lots of NSR!
Shannon

Alcohol Consumption and Risk of Atrial Fibrillation:
A Prospective Study and Dose-Response Meta-Analysis

STOCKHOLM, SWEDEN. We have covered a number of studies in recent years on the association of alcohol consumption and risk of triggering AFIB, and now this recent prospective study of 79,019 Swedish men and women who were free of AFIB at baseline, and then followed for just shy of 860,000 person-years from 1998 to 2009, was combined with a meta-analysis of nine separate prospective studies from 40 countries taken largely from work in Denmark, Sweden and the United States. The prime intent was to take an in-depth look at the association of total alcohol consumption, patterns of use and types of alcohol with new onset AFIB, while attempting to establish a real-world dose-response relationship in order to potentially give a practical guideline for people to follow.

First and foremost, the aim is to avoid alcohol-induced episodes whenever possible, and secondarily to gauge what might be a reasonably safe level of consumption for those for whom total abstinence feels like a significant limitation to their life style. In addition, insights are given as to which alcoholic drinks are most likely to cause trouble with our heart rhythm.

With only a handful of clear patient-controllable life-style modifications for minimizing the occurrence of AFIB documented in the literature, excess alcohol consumption has long been universally recognized at near the top of the list as a significant trigger and instigator for both first time, and recurrent, AFIB episodes. Uncontrolled hypertension, increasing age, pre-existing cardiovascular disease, diabetes, obesity, sleep apnea and smoking are all additional prime candidates for increased risk of AFIB.

Prior to this combined meta-analysis and new study, which amounts to the largest such study to-date, the collective statistical power was lacking to clearly differentiate weaker associations between light to moderate drinking and new onset AFIB. Indeed, before this degree of sensitivity, most previous reports tended to emphasize binge drinking and clearly excessive consumption levels as obvious culprits. Yet now, the authors were able to unlock solid associations between total amounts or alcohol, patterns of use as well as type of alcoholic drinks and their likelihood of spoiling the party with a rude and unwelcomed associated bout of arrhythmia.

Results

Out of this 79,019 Swedish cohort, 7,245 were hospitalized for AFIB over the 12-year study term, from hospital intake registries. Looking at these new AFIB patients and comparing all those consuming <1 drink per week, to those who imbibed between 15 to 21 drinks-week, the later had a 14% increased risk of AFIB, and those drinking >21 drinks a week had a 39% increased relative risk compared to the <1 drink/week near teetotalers.

Consumption level of two drinks a day was not strongly associated with initial triggering of AFIB, yet a finding in agreement with the previous prospective studies when combined in meta-analysis, and from which collective view, a linear dose response relationship between alcohol consumption and AFIB was noted, they were able to demonstrate that even relatively small doses of alcohol are, indeed, associated with a small, but still significant, added risk of new onset AFIB.

Beer drinkers get a bit of a break as there wasn't a strong association with new onset AFIB in the study in all three classes of beer with alcohol (<2%) by volume in class one, (2.8% to 3.5%) in class two and (> 3.5%) in class three, even with moderately higher levels of weekly consumption. However for liquor and wine, more than 14 drinks a week was strongly associated with increased risk of new onset AFIB.

Binge drinking, which equaled >5 drinks on a single occasion, and which 18% of the large Swedish cohort identified with, is associated as well with a significant 29% increase risk for AFIB, a well known connection that comes as no surprise to most readers of our newsletter.

Broken down by increment of consumption, there is an 8% increase risk for new AFIB for each additional increment of 10gram/day of alcohol consumption, or per drink per day (assuming a 12 gram

equivalent of pure alcohol per drink). Think about that next time the urge arises to down a few glasses of wine or a couple of vodka tonics in a row if you are prone to AFIB to begin with.

Clearly there is no one-size-fits-all formula for all afibbers with regard to alcohol intake; some cannot handle half a beer while others can tolerate several or more drinks on occasion without causing problems. However, the message is clear from such a large meta-analysis, and confirms our long offered advice at *The AFIB Report,* that alcohol remains a key risk factor for new and recurrent AFIB episodes, ranging from a relatively small risk to a very significant one depending on dose and type of alcohol; with both wine and liquor carrying approximately equivalent per drink risks, beer a good deal less so, and binge drinking should be absolutely out of the question for anyone with a fibrillating heart tendency.

Larsson SC. Drca N. Wolk A. ***Alcohol Consumption and Risk of Atrial Fibrillation: A Dose Response Meta-Analysis, J. American College of Cardiology July 2014;64, Vol 3: 281-9. http://dx.doi.org/10.1016/j.jacc.2014.03.048***

Conen D. Albert CM. ***Editorial Comment: Alcohol Consumption and Risk of Atrial Fibrillation: How Much is Too Much? J. American College of Cardiology July 2014;64, Vol 3: 290-2***

Editor's comments: If there remained any remote doubt about the connection between AFIB and alcohol, this study puts the last nail in that coffin. While moderate beer drinkers get somewhat of a reprieve from these results, that too is relative, and each person who wishes to regularly consume even beer, but especially liquor and wine, should heed the limits suggested. And at any signs of triggering an episode, or increased ectopic activity, during the day of, or after, even minor to moderate consumption of alcohol, please take to heart your bodies signal to lower any future limits. And some will do best to abstain altogether, especially when their AFIB is still prone to triggering.

Keep in mind that most of these stats are related to alcohol's impact on initiating first time AFIB. Once paroxysmal AFIB is well entrenched, common sense and a wealth of anecdotal experience by afibbers everywhere indicate even less tolerance for exposure in an effort to reduce repeat triggering. Even for those of us for whom AFIB is a receding memory after a successful ablation process, wisdom and experience would support sticking to these dose/risk consumption guidelines from this large new study.

Nevertheless, there is some leeway and room for experimentation for those who value including alcoholic libations as part of one's life. Just keep that 8% added risk per drink in your awareness whenever the urge to reach for just one more comes to mind. Taking that into consideration, at least, and thus keeping things on the safer side of caution, is no doubt the better part of valor when it comes to keeping things quiet for active afibbers.

Effect of Years of Endurance Exercise on Risk of Atrial Fibrillation and Atrial Flutter

OSLO, NORWAY. In this summary, we look at two recent large studies out of Scandinavia that underscore the rising consensus from previous investigations on long term intensive endurance exercise and its association with AFIB.

Not unlike our revisit to the potential impact alcohol can have on AFIB in our first report above, in past issues we have also examined the strong association between excessive endurance exercise and increasing risk for AFIB. A wise and informed choice in exercise method is yet another modifiable life-style choice that can make a big difference in reducing AFIB burden in the lives of those who include a thoughtfully designed and robust, yet modest intensity regular exercise program for overall good health, including cardiovascular health, in particular.

First, let's look at a recent retrospective study out of Norway that adds important new insights into the dose-response relationship between regular normal levels of endurance exercise and risk of AFIB, to give practical actionable guidance, not unlike the dose/risk guidelines we learned about with alcohol use above, when designing a safe and supportive fitness program that avoids adding excess stressors, inflammation and possible increased cardiac fibrosis to the equation. All of those stressors related to

excess endurance exercise can encourage new onset or recurrent AFIB as a result of overdoing a good thing.

This study also differentiates between AFIB and atrial flutter over cumulative years from 1999 through 2012, from normal, not excessive, levels of endurance exercise as seen in this large group of older Norwegian men (?53 years old). Most previous studies investigating the association between exercise and AFIB have examined intensive athletes in action, as opposed to the possible connection between typical leisure time exercise in the general population and AFIB, as is explored in these two studies.

The study was divided into two cohorts. The first group including a net of 2,366 men possessing a Norwegian postal address and born after 1959, who participated in the challenging Birkebeiner 54km cross-country ski race in 1999, and subsequently responded to the 2012 study questionnaire. The second cohort consisted of a net 1,179 men who did not report any arrhythmia during the final Oslo survey in 2009, and which represents 51% of the total of 3,545 men who were examined as part of the population-based Oslo Health Study covering the period from 2000 to 2001, including the final survey in 2009. All of these men had given consent for future contact and study participation.

In addition, all 494 men who reported arrhythmia in the 2009 Oslo survey were included to maximize the number of end-points. This group was further titrated down by eliminating those who did not respond to this most current 2012 questionnaire (N=144), and those who were found to have no arrhythmia on testing (N=167), leaving a net number of 183 men from the Oslo Health Study eligible for inclusion and who both responded to the questionnaire and had documented arrhythmia.

Results-Norwegian study

In total, 489 men reported AFIB in the 2012 questionnaire; among the skiers the prevalence of self-reported AFIB was 12.5%. The weighted-prevalence among the participants in the Oslo Health Study cohort was 10.3%. A host of covariates were accounted for by questionnaires.

Cumulative years of regular exercise were associated with a gradual increased risk for AFIB with an *'adjusted odds ratio'* (aOR) of **1.16** (95% CI 1.06 to 1.28) per 10 years of exercise. Among the skiers the aOR was **1.16** (95% CI 1.00 to 1.36) and among men from the Oslo Health Study aOR was **1.20** (95% CI 1.06 to 1.35).

Regular endurance exercise was also associated with a gradually increased risk of atrial flutter with an aOR per 10 years of exercise of **1.42** (95% CI 1.20 to 1.69), and did not differ between the two cohorts of cross country skiers and Oslo health study men.

Men with a history of long-term regular exercise tended to be younger, taller and had lower body mass index (BMI), a higher educational level and, as expected, this group had a lower prevalence of concomitant heart disease, hypertension and diabetes than did those men who had never exercised regularly. This finding is consistent with the well-established overall health benefit of regular modest exercise.

While the underlying mechanism and pathophysiology of exercise-induced arrhythmia is not yet fully defined, increases in inflammation, autonomic parasympathetic tone imbalance and atrial remodeling with progression of atrial fibrosis are several of the leading suspected culprits behind this clear association. And although this study's design did not include a search for underlying mechanisms for exercise induced AFIB, their results did support that the dose/response relationship does play an important role in the underlying pathophysiology of both AFIB and atrial flutter.

Of interest, the prevalence of AFIB was higher than expected in the youngest, and lower than expected in the oldest participants in their study, and this estimated effect increased slightly in sensitively analysis after excluding men greater than 75 years old.

These findings, while looking at the same issue from a somewhat different angle, also resonate with another important, and very large recent study, from Stockholm Sweden on *'AFIB associated with different levels of activity over different age groups'*, which we briefly summarize next.

Results-Swedish study

This Swedish study showed that moderate to high intensity physical activity, such as leisure-time exercise of more than 5 hours a week at the age of 30 years old, increased relative risk (RR) by 19% for developing AFIB later in life. By contrast, low to moderate intensity transportation-style physical activity like walking or bike riding of more than 1 hour total per day later in life at older age decreased risk of new onset AFIB. In fact, there was no increase in AFIB risk with walking or biking normally used for transportation at any age.

Both of these studies offer noteworthy additions to our current knowledge. The first Norwegian study showing a clear graded dose-response relationship between cumulative years of regular endurance exercise and risk of AFIB in men ?53 years of age. And for the first time, a corresponding increased risk for atrial flutter under the same conditions was found.

The Stockholm study is the largest, by far, looking at the AFIB/exercise association to date in a general population comprised of 44,010 men followed for a median of 12 years. The results showed a complex association between physical activity and development of AFIB. A potential explanation for the different impact of exercise on AFIB risk, depending on age, could be because in older ages the positive effects of physical activity on risk factors for AFIB dominate over the potential negative effects. Also, on average leisure-time exercise may be of lower intensity at an older age than similar type exercise at 30 years old.

Myrstad M, et al. ***Effect of Years of Endurance Exercise on Risk of Atrial Fibrillation and Atrial Flutter. Am. J of Cardiology 2014: http://dx.doi.org/10.1016/j.amjcard.2014.07.047***

Drca N, Wolk A, Jensen-Urstad M, et al. ***Atrial Fibrillation is Associated with Different Levels of Physical Activity at Different Ages in Men****. Heart 2014;100:1037-1042 http://dx.doi.org/10.1136/heartjnl-2013-305242 , http://dx.doi.org/10.1136/heartjnl-2014-305780.*

Editor's comments: The take home message from both of these Scandinavian-based research efforts is that low to moderate intensity life-long exercise is the way to go long term. From multiple studies now, we are getting the clear message that prolonged intensive endurance exercise, in particular, when begun earlier in life and carried on with moderate to high intensity for many years to decades, not only increases the potential for cardiovascular disease, but also adds to an increased risk of developing AFIB/Flutter later in life.

Low to moderate levels of endurance exercise more typical for transportation, such as long walks and bike riding around town and to and from work, only seem to confer health benefits for the heart as well as body and mind as a whole. Just realize that a voluminous amount of data now strongly implies that once you pass a certain threshold of intensity of endurance exercise for the long term, you very likely risk reversing many of the health benefits conferred by more moderate exercise programs. Typically, when one gets too intense for too long with challenging their bodies, they wind up doing it for other reasons and motives than strictly good health, which we see can slowly be sacrificed in the bargain.

Rivaroxaban (Xarelto) vs. Warfarin/VKA for Cardioversion in AFIB:
The X-VERT Trial

BARCELONA, SPAIN. We review here an important new development reported at the recently completed European Society of Cardiology (ESC) 2014 Congress in Barcelona from an open-labeled, multinational, randomized trial exploring the efficacy of *Xarelto* and, by extension, other Factor Xa inhibitor novel oral anticoagulants (NOAC) as a substitute for w*arfarin* and other *vitamin K antagonist (VKA)* anticoagulants. Lead researcher, Dr. Riccardo Cappato (University of Milan) highlighted the results from this first prospective comparison between a NOAC, in this case *Xarelto*, and w*arfarin/VKA*, in the specific setting of elective DC-cardioversion (ECV) for AFIB.

A total cohort of 1504 patients with hemodynamically stable non-valvular AFIB of 48-hour or unknown duration, were assigned to either an early **(1 to 5 days)** or delayed **(21 to 25 days)** cardioversion strategy via a randomized 2:1 ratio for the larger group, using once a day *Xarelto* (**20mg/day)**, or **(15mg/day)** for patients having creatinine clearance **(30-49ml/min)**, compared to the second group using standard titrated *warfarin* or *VKA* equivalent.

Those who could not be cardioverted within the allotted group time window were continued on study protocol until they had either ECV at a later visit in the treatment phase, or experienced spontaneous conversion to NSR as happened to **117** patients in the total study cohort. In total, **115** patients had their ECV postponed to a later date (*Xarelto* = **21** and w*arfarin/VKA* = **94**).

Both groups consisting of the entire trial cohort continued on the selected anti-coagulation therapy after ECV for six full weeks.

Warfarin/VKA treatment was considered acceptable if the INR (international normalized units) was held steady in the therapeutic range of 2 to 3 for at least three weeks, as has been standard of care anti-coagulation requirements for many years prior to having an AFIB-related cardioversion. Of note, 77% of the total number in both the early and delayed *Xarelto* group had their ECV within the allotted time window, while only 36.3% of the total w*arfarin/VKA* group were cardioverted within their groups target time range (p<0.001).

An obvious primary reason for w*arfarin/VKA* patients to postpone their ECV beyond the selected time frame was from failure to achieve a stable therapeutic INR for three consecutive weeks within the target window.

The bottom-line results from this trial demonstrated that both *Xarelto* and w*arfarin* were comparatively effective and safe, which is important news for practical clinical decision-making by cardiologist and ER physicians everywhere.

The primary efficacy outcome was a composite of stroke, TIA (transient ischemic attack) peripheral embolism, MI (myocardial infarction) and cardiovascular death. The primary safety outcome was measured by major bleeding. A primary efficacy outcome occurred in **5** patients (two strokes) out of **978 (0.51%)** in the *Xarelto* group, and in **5** patients (two strokes) of **492 (1.02%)** from the w*arfarin/VKA* group with a risk ratio **(RR) =0.50; 95% CI (0.15- 1.73)**.

In the *Xarelto* group, four patients **(0.71%)** experienced a primary efficacy complication after early ECV, and only one **(0.24%)** after following delayed ECV. In the w*arfarin/VKA* group, three patients **(1.08%)** had primary efficacy event after early ECV, and two patients **(0.93%)** experienced such events following delayed ECV. Major bleeding occurred in six patients **(0.6%)** in the *Xarelto* group, and four **(0.8%)** in the w*arfarin/VKA* group.

Xarelto was also associated with a significantly shorter time to ECV, and the low number or patients failing to achieve adequate anti-coagulation prior to ECV at 3 weeks in the delayed group showed the NOAC's practical advantage compared to w*arfarin/VKAs* for elective cardioversion **(p<0.001)**

End Points	Xarelto, n = 978 (%)	Warfarin/VKA n= 472 (%)	RR (95% CI, Xarelto vs. VKA)
Primary Efficacy (a)	**0.51**	**1.02**	**0.5 (0.15 – 1.73)**
Primary Safety (b)	**0.61**	**0.80**	**0.76 (0.21 – 2.67)**
Net Clinical Risk (c)	**1.06**	**1.81**	**0.49 (0.14 – 1.69)**

(a) Stroke, transient ischemic attack, peripheral embolism, MI, or cardiovascular death
(b) Major Bleeding
(c) Stroke, non-CNS systemic embolism, TIA, MI, cardiovascular death, or major bleeding

(Table by Steve Stiles, Heartwire © Medscape 2014)

In the early ECV group, *Xarelto* administered at least 4 hours prior to ECV provided effective and safe anti-coagulation and results were consistent across all analysis sets.

While the authors of this trial noted that it was "underpowered to provide statistically rigorous results, and thus was primarily exploratory in nature", it does add significant data and insight to our current understanding around use of NOACS with ECV and provides a strong degree of "solid, methodologically sound evidence" for those physicians already using NOACs for cardioversion in place of w*arfarin* or another *VKA* drug.

Cappato, RD. et al, *Explore the Efficacy and Safety of Once-Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Patients with Nonvalvular Atrial Fibrillation Scheduled for Cardioversion (X-VERT)* ***Epub Ahead of Print: Eur. Heart J. http://dx.doi.org:10.1093/eurheartj/ehu367***

Editor's comment: It goes without saying that this is great news for all afibbers who may be in need of cardioversion to stop a pesky AFIB/Flutter episode. The pharmacological characteristics of these Factor Xa inhibitor NOACs, such as *Xarelto*, *Eliquis* and *Lixiana* (Endoxaban), should be particularly useful in the setting of elective cardioversion with their rapid onset of action, short half-life and predictable pharmacokinetics, all potentially greatly shortening the time when an ECV can be performed, even in cases of unknown AFIB episode duration. And hopefully, even more rigorous future studies will include persons found to have pre-existing thrombus or SEC (spontaneous echo contrast) 'smoke' in the LAA. Doing so, might thus help define how effective these new Factor Xa inhibitor NOACs can be at breaking down and dissolving such clots, and thus gaining even more flexibility in safely scheduling both drug therapy and elective cardioversion.

Portola Pharmaceuticals Announces Phase 3 ANNEXA-A Study:
Andexanet Alfa antidote for Factor Xa NOAC Eliquis (Apixaban)

SAN FRANCISCO, CALIF. On October 1, 2014 Portola Pharmaceuticals, who has been leading the race to develop an effective, fast-acting and safe reversal agent for the new NOAC Factor Xa inhibitor anticoagulant agents like Eliquis (apixaban), Xarelto (rivaroxaban) and the latest - soon to hit market - Lixiana (endoxaban), issued a preview of results on their 'Andexanet Alfa' antidote candidate, due for formal presentation at the American Heart Association 'Clinical Science: Special Reports' Sessions on November 17, 2014.

This, too, is big news of potential interest to a large majority of afibbers over the course of their lives. Most of our readers are aware of the big push, and rush, to bring these NOAC drugs to market. And many, including myself, felt this rush was done too prematurely before an effective reversal agent/antidote to the powerful blood thinning properties of these news drugs was widely available. This lack of such vital protection has caused a significant number of deaths and injuries, as well as reticence toward wider adoption of these otherwise promising drugs, by both patients and doctors alike.

As such, that 'Andexanet Alfa' has achieved fast track status with the FDA under its 'breakthrough therapy designation', should help insure it reaches wide market availability as soon as possible after completing FDA approval and certification. An investigational antidote for the oral thrombin inhibitor dabigatran etexilate sulfate (Pradaxa) also has been awarded FDA breakthrough status.

"Andexanet Alfa represents a potentially important advance for Factor Xa inhibitor anticoagulation patients who suffer a major bleeding event or those requiring emergency surgery" said William Lis, CEO of Portola.

"These highly statistically significant Phase 3 ANNEXA-A data demonstrate that Andexanet Alfa has the potential to be the first agent approved for Factor Xa inhibitor reversal. We anticipate filing a Biologics License Application with the FDA for Accelerated Approval at the end of 2015" said John T. Curnutte MD, PhD, president of research and development at Portola. "We expect to report additional data this year and next with other Factor Xa inhibitors in addition to apixaban, including rivaroxaban, endoxaban, betrixaban and enoxaparin (a low molecular-weight heparin)".

ANNEXA-A Design and Results

This randomized, double blind, placebo-controlled Phase 3 ANNEXA-A trial is evaluating safety and efficacy of Andexanet Alfa in reversing Eliquis-induced anticoagulation. Thirty-three older healthy volunteers were given 5mg Eliquis twice a day for four consecutive days and then the group was randomized in a 3:1 ratio to receive either an intravenous (IV) bolus of 400mg Andexanet Alfa, or to placebo. The study met its primary and secondary endpoints with a high statistical significance. Results showed that Andexanet Alfa immediately and significantly reversed the anticoagulation activity of Eliquis.

A second ANNEXA-A study of 32 healthy volunteers will be given Eliquis 5mg twice a day for four days and then randomized again in a 3:1 ratio; with 400mg IV bolus of Andexanet Alfa, followed by continuous infusion of 4mg/min for 120 minutes, or to placebo. These data reportedly will be available in early 2015. These results and reported safety look highly promising, though we must a wait for the full formal study data to be reported on November 17, 2014, to confirm that confidence.
http://money.cnn.com/news/newsfeeds/articles/globenewswire/10100784.htm

Editor's comments: Assuming these very promising Phase 3 results pan out fully in the coming year of trials, and with the fast tracking efforts of the FDA, it indeed looks very likely that a safe and effective reversal agent my be available to ambulances, ERs and trauma centers world-wide much sooner than I had dared hoped even just a few months ago.

And while such an approval will go a long way toward removing the prime barrier to wider adoption, and thus offer a much greater sense of safety around use of these new anticoagulants, it must also be underscored too that even when the antidote is fully in place, no one should forget that these are powerful drugs and blood thinners that we do not yet fully understand. As such, though this is entirely welcomed news, I do hope it will not make giving out these drugs so easy that they are handed out like popcorn to everyone who has a moment of arrhythmia. Only people who clearly meet the guidelines for use, irrespective of the antidote being approved or not, should be candidates for these new agents. The lack of an antidote, to date, has put a damper on more of those who are genuine candidates for use to begin therapy with these drugs, and that reticence may now soon be overcome.

Increased Mortality Associated with Digoxin in Contemporary Patients with AFIB:
Findings from the TREAT-AF Study

PALO ALTO & STANFORD, CALIF. From not long after the birth of this newsletter, and long before the majority of cardiologist and EPs became aware of it, founder Hans Larsen had alerted us all to the clear problems with digoxin, a long time favorite rate control drug for AFIB. Despite the long-time endorsement of digoxin in cardiovascular clinical practice guidelines, there has always been a surprisingly limited amount of solid data on the safety of this drug used in AFIB/Flutter.

More recent studies have increasingly called into question digoxin's role and safety in AFIB management, and the goal of this large investigation examining findings out of the retrospective cohort TREAT-AF study, was to evaluate the association of digoxin with mortality in AFIB.

TREAT-AF selected this cohort of patients from the US Department of Veteran Affairs (VA) healthcare system, which is the largest integrated healthcare system in the US. The study cohort included 122,465 patients with mean age of 72.1 ± 10.3 years: 1.6% were women in this expected male dominated pool of patients. From a total of 122,465 subjects over 353,168 person-years of follow-up, this analysis included the largest AFIB cohort to date addressing the issue of digoxin therapy's association with mortality in patients with newly diagnosed AFIB.

Bottom-line

Accounting for a number of key confounders as well as adjusting for sensitivity to unmeasured confounding, the study results demonstrate that digoxin is, indeed, associated with increased risk of

mortality in afibbers. The raw data supports the same conclusion, and these observations were consistent across all sub-groups and were independent of drug adherence, kidney dysfunction, heart failure, or concomitant therapy with beta-blockers or amiodarone.
Turakhia MP, et al. ***Increased Mortality Associated with Digoxin in Contemporary Patients with AFIB: Findings from the TREAT-AF Study****. JACC 2014: http://dx.doi.org/10.1016/j.jacc.2014.03.060*

Editor's comments: Those readers who wish to dig deeper into the study details can access them from PubMed or directly from the JACC link above. This is solid data from a well run large study that not only builds upon a wealth of recent prior investigations that collectively confirm that digoxin has little to no role as a front line rate control drug used for AFIB/Flutter. Surely, all guidelines will be updated to reflect this, by now; well-respected and followed advice in cardiovascular and EP circles everywhere. Thank you Hans for blazing this trail.

AFIB Ablation Patients Have Long Term Stroke Rates Similar To Patients Without AFIB Regardless of CHADS2 Score

SALT LAKE CITY, UTAH. We wrap up this issue with a brief review of an exciting new study from the renowned Utah EP group, Intermountain Heart Institute at Intermountain Medical Center, with such well-known EP ablationists and researchers as Drs. Jared Bunch, Peter Weiss and John Day, et al, examining the long term impact of AFIB ablation on stroke risk and rates. Using their large on-going prospective Intermountain AFIB Study database of patients enrolled in this major health care system in Utah and the rocky mountain region as the pool of study participants.

The key objective of the study was to determine if ablation of AFIB/Flutter reduces stroke rates across all risks groups. A total of 4,212 consecutive patients who underwent AFIB ablation were compared (via a 1:4 ratio) with 16,848 age/sex-matched controls with AFIB who had no ablation, and to 16,484 age/sex-matched controls who have never had AFIB.

Results

Across the total study population, AFIB ablation patients have a significantly lower risk of stroke compared to AFIB patients who do not undergo ablation, independent of baseline stroke risk scores. In addition, the authors found that the stroke risk over time of AFIB patients treated with ablation was similar to patients with no history of AFIB at all. Furthermore, AFIB ablation patients with moderate to high risk CHADS2 scores prior to and after ablation, in which warfarin was discontinued, do not show a higher stroke risk compared to those in whom warfarin was continued.

These are powerful findings, no doubt, and reassuring … though perhaps not surprising … for not only those of us who have completed a successful ablation process, but also for those contemplating taking that step toward having an expert ablation to get the upper hand on what is so often an exhausting struggle dealing with this lousy condition when it is active in one's life. These results give additional positive and compelling evidence as well toward how, and to what degree, AFIB ablation might alter the natural course and history of AFIB, including how it relates to cerebral vascular accidents (CVA).

Note: this study took on all comers including, no doubt, a significant majority of patients with some degree of structural cardiovascular disease and/or hypertension, and likely a minority with true lone AFIB or very low inherent stroke risk.

Keep that in mind when looking at the, nevertheless, still very impressive stroke risk reduction in the ablation subgroup. Past studies have indicated a negligible stroke risk for afibbers who have truly 'lone AFIB' with a CHADS2 of 0 to 1, and this study likely lacked the power to underscore that variable.

Let's look at two tables below from the study results, which clearly tell the story.

Age-based long-term stroke risk AFIB pts. with ablation versus AFIB pts. without ablation

Age	AF, no ablation	AF, w/ablation	P value	Univariate HR for ablation*	Multivariate HR for ablation*
<60, n=5638	3.6%	1.3%	< .0001	0.38, P< .0001	0.38, P< .0001
60-69, n=5804	5.6%	2.9%	< .0001	0.50, P< .0001	0.59, P< .005
70-79, n=7082	8.7%	3.8%	< .0001	0.42, P< .0001	0.50, P< .0001
=80, n=2536	8.6%	5.8%	.07	0.55, P = .009	0.72, P< .17

* UHR (Univariate Hazard Ratio), MHR (Multivariate Hazard Ratio)

CHADS-2-based long-term stroke risks – No AFIB, AFIB pts. w/ablation & AFIB pts. w/o ablation*

CHADS2	No AFIB	AFIB, no ablation	AFIB, ablation	P value
0	2.6% (178 of 6902)	3.7% (220 of 6017)	1.6% (26 of 1628)	< .0001
1	3.0% (144 of 4772)	5.4% (243 of 4477)	1.9% (20 of 1050)	< .0001
2	4.3% (129 of 3015)	7.1% (217 of 3072)	2.2% (15 of 696)	< .0001
3	7.4% (108 of 1452)	9.0% (174 of 1939)	6.1% (21 of 512)	.06
4	10.7% (52 of 484)	17.6% (152 of 864)	9.1% (20 of 220)	< .0001
=5	13.9% (31 of 223)	18.6% (89 of 479)	13.2% (14 of 106)	.18

*CHADS2 stroke risk across 3 age/sex matched subgroups: 1 No AF, 2 AF w/ablation, 3 AF w/o-ablation

Notice the significant reduction in stroke risk in former afibbers now rendered free of AFIB, or with greatly reduced AFIB burden, after a successful ablation process and across all age groups and all formal CHADS2 stroke risk stratification. Even compared to those age/sex-matched controls who never had AFIB, the former afibbers … now ablated … not only are in the same stroke risk range as those without AFIB, but with a slight edge, though perhaps not a statistically significant advantage.

Perhaps one logical rationale for the slight edge shown here for the ablated AFIB group over those who never have had AFIB, is the likely better care taken by those who have gone through an ablation process in reducing those other stroke risk factors beyond AFIB itself, as it is common for those of us on this journey who have taken a comprehensive approach to managing AFIB, to naturally learn how to better take care of our overall health in the process.

Bunch JT, et al. ***Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. Heart Rhythm 2013;10:1272-1277*** ***http://dx.doi.org/10.1016/j.hrthm.2013.07.002***

Editor's comments: This very well thought-out and executed study out of Utah showing a positive practical long term reduction in stroke risk for those who have undergone successful AFIB ablation provides an apropos bookend to this Oct/Nov issue of *The AFIB Report*. While most of the topics explored in this issue pertain to life-style modifications that, when made with well-armed knowledge and motivation, can greatly reduce AFIB burden in many cases, it's nevertheless often the case that the best approach, longer term, is a well-rounded comprehensive and balanced effort to manage AFIB in our lives in order to reduce its presence to the bare minimum possible.

Such a comprehensive strategy almost always works best when combining the best of dietary and nutritional repletion with stress reduction and life style choices, plus medication when warranted, to reduce blood pressure, obesity, avoid excess alcohol, moderate caffeine and address sleep apnea, diabetes and metabolic syndrome when present. And yes, for many of us, lasting success over AFIB often requires the key step of an expert AFIB ablation process at the right time, and with the most experienced operator we can find.

Please join us again in December for more of such heart care insights and latest findings from medical science that can help us reclaim, and sustain, a stable heart and a more rewarding life.

Shannon Dickson

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THE AFIB REPORT is published 6 times a year by
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