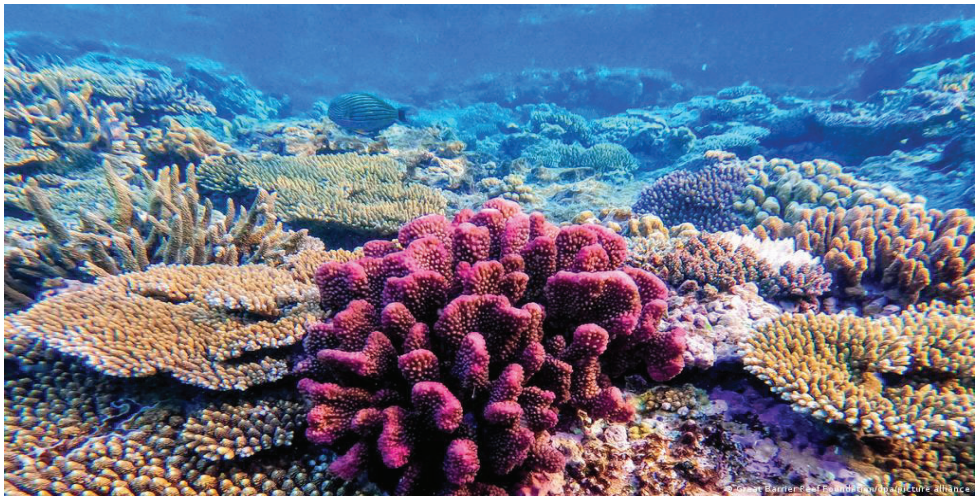
November 2022 ONE YEAR ANNIVERSARY Issue

Talk of the Town

-A Midtown Journal Club Newsletter



Of Polyps and Men:

Do colonoscopies Have *Population-Wide* Benefit?

Article by Mitchell Belkin (PGY1)

Colon cancer is the second leading cause of cancer-related deaths globally. While colonoscopy is considered the gold standard for colorectal cancer screening, its effect on the risks of colorectal cancer and related deaths has not been studied in an RCT.

The **NordICC** trial was designed as a randomized controlled trial to evaluate the effectiveness of colonoscopy as a **public health** intervention. The NordICC trial enrolled 55-64 year old adults who were selected from population registries in Poland, Norway, Sweden and the Netherlands. Participants underwent an uneven randomization (1:2 ratio) to participate in a screening program (invited group) or the standard of care in the respective country (usual-care group). Presumably, the uneven randomization was done because it was easier to recruit control patients who would undergo usual-care than the screening program.

Participants were excluded if they died or were diagnosed with colorectal cancer prior to entering the trial. They were followed for 10 years to determine the risk of colorectal cancer and related death (primary endpoints), as well as death from any cause (secondary endpoint). Overall, 28,220 participants were in the invited group and 56,365 were in the usual care group. All had median 10-year follow-up data. Overall, 42% of participants who were invited to undergo screening colonoscopy actually had a colonoscopy (the per protocol analysis group). However, there were differences in country participation rates: for instance, Norway had 60.7% and Poland had only a 33% participation rate.

<Learning Obejectives>

- What are the differences between Intention-to-Screen (ITS) and Per-Protocol (PP) analyses?
- How do patient-specific benefits and population-wide benefits differ?

Of note, both the **intention-to-screen** (ITS) and **per-proto col** (PP) analyses were conducted. As a reminder, an ITS analysis includes the results from ALL patients regardless of whether they completed the intervention as designed--whereas a PP analysis only examines the patients who finished the trial interventions as directed ("per protocol"). This distinction is important, because those who actually undergo a colonoscopy may differ from those who do not (for instance, in regards to education, health consciousness, motivation, and perhaps rates of colon cancer risk, such as family history).

Furthermore, since the two analyses are asking two different questions, they should be interpreted differently. For instance, results of an ITS analysis will be useful for **policymakers,** because it is asking the question, "Is this screening program itself useful (taking the dropout patients into account)?" On the other hand, a PP analysis may be more useful for a **practicing physician**, because it is asking the question, "Is this screening test itself useful *if* my patient follows my driection?" Results of an ITS and a PP analysis will not differ significantly if the number of "dropout" patients are low; but in screening trials such as **NordICC**, the results were very different given the very low number of compliance rates.

NordICC showed that amongst the **ITS** population, 259 (0.98%) participants in the invited group had colorectal cancer and 622 (1.20%) participants had colorectal cancer in the usual care group, meaning there was a statistically significant risk ratio of 0.82 [95% CI 0.70-0.93]. However, the death from colon cancer (0.28% vs 0.31%; RR 0.90 [0.64-1.16]) and death from any cause (11.03% vs 11.04%; RR 0.99 [0.96-1.04]) were not significantly different. On the other hand, in the **PP** analysis, the risk of colorectal cancer at 10 years decreased from 1.22% to 0.84% (RR 0.69). As for the risk of death from colorectal cancer at 10 years, there was an absolute risk reduction from 0.30% to 0.15%. The number needed to screen to prevent one colon cancer death was 666. As for adverse events, no patients in this analysis had a perforation. Major bleeding occurred in 15 patients (0.13%). This was defined as any bleeding that warranted treatment – and all were treated endoscopically without further therapy warranted.

In summary, colonoscopy is a safe procedure with a very low risk of major adverse events. In the intention-to-screen analysis, a colorectal cancer screening program reduces risk of colon cancer diagnosis but not death, suggesting limited effectiveness as a public health intervention. By contrast, in the per protocol analysis death from colon cancer was reduced by 0.15%, which suggests real—albeit mild—efficacy to patients who undergo the intervention. Given the expense of colonoscopies as an intervention as well as the NNT (666 colonoscopies per life saved), colonoscopy as a **public health intervention** is less beneficial than previously believed.

CHOOSE YOUR FIGHTER:

Low-Molecular Weight Heparin

VS

ASPIRIN

FOR ORTHOPEDIC PATIENTS

Article by Spyridon Ntelis (PGY2)

It is not uncommon for orthopedic surgeons to recommend aspirin monotherapy for deep venous thrombosis prophylaxis after a procedure. Aspirin has some benefits, including ease of administration and lower cost compared to low-molecular-weight heparin. However, limited evidence exists regarding the efficacy and safety of aspirin as a sole prophylactic agent.

The **CRISTAL** study was a cluster-randomized, cross-over, partially-blinded trial, across 31 hospitals in Australia. The aim of the study was to assess if aspirin monotherapy is non-inferior to LMWH to prevent symptomatic venous thromboembolism after total knee or total hip arthroplasty for osteoarthritis. Clusters were hospitals performing 250+ procedures per year. A total of 9711 patients aged ≥18 (median age 68 years) were enrolled in this study, 5675 in the aspirin group and 4036 in the enoxaparin group. Exclusion criteria were preoperative dual antiplatelet therapy and anticoagulation treatment (warfarin or DOAC), as well as a contraindication to either of the compared agents, including allergy and bleeding diathesis.

Hospitals were randomized to give 100 mg of aspirin per day or 40 mg of LMWH per day for 35 days after a total hip arthroplasty and for 14 days after a total knee arthroplasty. Being a cluster-randomized trial, randomization was done at the **hospital level**. Cross-over occured after the patient enrollment target had been met for the first group. All 31 hospitals were initially randomized and 16 of them crossed over prior to trial cessation. Participating hospitals and patients were not blinded, contrary to investigators and the data and safety monitoring board.

The primary outcome was symptomatic VTE within 90 days of surgery. Symptomatic VTE occurred in 256 patients, including pulmonary embolism (79 cases), above-knee DVT (18 cases), and below-knee DVT (174 cases). The symptomatic VTE rate in the aspirin group was 3.45% and in the enoxaparin group was 1.82% (estimated difference, 1.97%; 95% CI: 0.54%-3.41%), which failed to meet the criterion for noninferiority for aspirin and in fact showed significant superiority for enoxaparin (P = 0.007). Due to this finding of enoxaparin superiority, participant enrollement was stopped at 20 months, and only 9203 (95%) patients completed the trial.

A number of limitations were aknowledged. First, some hospitals had a low patient enrollement rate, which raises concern for selection bias. In addition, the loss of follow up was 5.2%, which could have resulted in loss of significant data, and the early termination of the trial resulted in less precise outcomes. The lack of blinding of treating physicians also may have affected the rate of VTE diagnosis in either group. Most importantly, 15% of the included patients were already on aspirin therapy at the beginning of the trial. Those in the aspirin group continued the same treatment postoperatively with no adjustment in dosing, while those randomised in the LMWH group continued aspirin with the addition of enoxaparin, which could have influenced the finding of enoxaparin superiority. Nevertheless, the study findings provide good evidence to support the use of enoxaparin over aspirin for postoperative DVT prophylaxis after THA and TKA.

Supine vs SITTING:

Which is Better for Orthostatic Hypotension?

Article by Elvina Yunasan (PGY2)

When you assess orthostatic blood pressure, do you measure blood pressure from supine to standing position or sitting to standing position? A recent ancillary analysis from **Study to Understand Fall Reduction and Vitamin D in You (STURDY)** by Juraschek et al. can help us to understand the relationship between supine vs. sitting BP measurement with falls and orthostatic symptoms.

As its name suggests, **STURDY** was originally a doubled-blinded RCT that tested the beneficial effect of Vitamin D on fall risk. An additional analysis was performed to compare supine to standing vs. sitting to standing BP measurement and its relationship with prevalence of orthostatic hypotension, incident of falls, and orthostatic symptoms. The trial included adults aged 70 years and older with low vitamin D (10-29 ng/ml) and elevated fall risk (2 or more falls or injurious fall in the past year, fear of falling, difficulty maintaining balance or use of an assistive device). Adults with cognitive impairment, hypercalcemia, kidney stones, consuming >1000 IU/day of vitamin D3 supplements or >1200 mg/day of calcium supplements were excluded. For the ancillary study, both supine to standing and sitting to standing BP measurement were obtained in 534 participants for 4 times during the 2-year study.

Orthostatic hypotension was defined as a drop in SBP of at least 20 mmHg, or a drop in DBP of at least 10 mmHg was more commonly seen in the supine protocol (15 %) compared to in the seated protocol (2.1%). Furthermore, supine OH was significantly associated with self-reported syncope symptoms such as fainting, blacking out, seeing spots and room spinning during the previous 30 days ($p < 0.03$), while sitting OH was not associated with any syncope symptoms ($p \geq 0.40$).

This study comes with multiple limitations. First, researchers of this study admitted that the sample size of the study is possibly not enough to detect a significant association of falls with supine vs sitting OH, given there is an

overlap of the confidence interval for the associations of OH with falls between seated and standing OH. Second, BP measurements during standing were performed with a different protocol. In the sitting protocol BP measurements were performed 1 minute after standing, whereas in the supine protocol, BP measurements were immediately performed after both feet touched the ground and 3 minutes after standing. Third, supine protocol measurements were always performed after the seated protocol assessment. BP results could be impacted due to diurnal variation of BP. Fourth, self-report syncope symptoms may be subject to recall bias. Lastly, as an observational study, we have to remember that this study is prone to confounders and cannot be used to demonstrate causality.

In summary, the results suggested that supine to standing BP measurement is more sensitive for detecting orthostatic and potentially more predictive of falls than sitting to standing position. If you have been checking orthostatic BP from a sitting position, maybe you should consider starting from a supine position instead.

Lifestyle Medicine

What's the Deal with Intermittent Fasting?

Article by Austin Burns (PGY1)

Despite innumerable global campaigns to address it, obesity continues to be a major global public health issue that has led to the investigation of new interventions to promote weight loss. Lifestyle modifications underpin most current weight loss strategies even though calorie restriction has historically led to only modest initial weight loss and difficulties maintaining reduced weight.

One technique that has recently become increasingly popular is time-restricted eating, a form of intermittent fasting that restricts consumption of calories to a shortened time period each day due to the theory that humans have evolved to go hours to days without food. Initial studies have shown that time-restricted eating may lead to weight loss for patients with obesity, but the **long-term effects** and impact on weight maintenance have not been fully characterized.

In the study **"Calorie Restriction with or without Time-Restricted Eating in Weight Loss"** (Liu et al. 2022), the investigators compared a calorie-restricted diet *with* time limitations against a diet with the same calories over 24 hrs but *without* time limitations. 139 adult patients from Guangzhou, China with a BMI between 28-45 were enrolled and randomly assigned to either group in after 1:1 matched randomization., for a study period of 12 months. Individuals were excluded if they had acute or chronic viral hepatitis, malignancy, diabetes, current smoking, serious CVD within the past 6 months, planning pregnancy, or used medications that affected weight or energy balance. Diets in both groups were intended to represent 75% of the participants daily caloric intake at baseline while maintaining appropriate macronutrient proportions. Participants in the time-restricted eating group were instructed to consume their calories between 8:00 a.m. and 4:00 p.m. each day, while the control group had no time restrictions. Participants also received dietary counseling throughout the trial, including caloric intake tracking, telephone calls and messages, as well as regular meetings with a health coach. The study was done for a total of 12 months.

The primary outcome of this study was the difference between the two groups in change from baseline body weight. Secondary outcomes included changes in waist circumference, body fat, body lean mass, quality of life, and cardiometabolic risk factors including plasma glucose levels, insulin sensitivity, serum lipids, and blood pressure. The mean weight change over the study period was -8.0 kg for the time restricted group and -6.3 kg for the calorie-restriction alone, which was not significantly different between groups (p=0.11). Participants in both groups also had similar reductions in waist circumference, BMI, body fat mass reduction, and loss of lean mass over the study period. Both groups also demonstrated reduced blood pressure and cardiometabolic risk factor levels that were not significantly different.

Therefore, the authors concluded that time-restricted eating with caloric restriction was **not** superior to caloric restriction alone in the primary or secondary outcomes measured. These findings indicate that most of the beneficial effects of intermittent fasting did not result in increased weight loss or improvement. Outcomes appear to be a result of **caloric restriction itself**, not time-specific caloric intake. Of note, this study benefited from good participant adherence in both groups, which had been a limitation of prior studies investigating weight loss strategies.

While this trial indicates that time-restricted eating may be viable for weight loss in patients who have struggled with other calorie-restriction strategies, there were a number of limitations that could reduce generalizability. For example, patients with diabetes or cardiovascular disease were excluded, all participants were recruited from a single city, and physical activity and energy expenditure were not measured.

*Dapa*gliflozin "DELIVER"s Results for HFpEF/HFrecEF

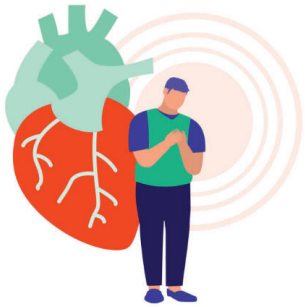
Article by Aleksan Kachatryan (PGY3)

SGLT2 inhibitors have been consistently shown to reduce the risk of death and other adverse outcomes in HFrEF and HFpEF, regardless of the presence or absence of type 2 diabetes mellitus. Evidence regarding treatment effect in patients who recovered from a very reduced EF to a mildly reduced range (40-60%) or above (60%) is still under investigation.

The recent **DELIVER** study aimed to test the effects of Dapagliflozin in patients at this mildly reduced or preserved EF range. It was designed as a multinational double-blinded RCT that recruited pat-

ients of at least 40 years of age, stabilized heart failure, with or without type 2 diabetes mellitus, left ventricular ejection fraction of more than 40% even if the patient had EF<40% in the past, evidence of structural heart disease, and an elevated natriuretic peptide level. A total of 6263 patients were randomized: 3131 received Dapagliflozin 10 mg and 3132 received a placebo in addition to standard therapy. The patients were observed over a median period of 2.3 years.

The primary outcome of the DELIVER study was a composite of worsening heart failure or cardiovascular death. Secondary outcomes were the total number of worsening heart failure events, change from baseline in the total symptom score (KCCQ-TSS) at month 8, cardiovascular death, and death from any cause. Results were reported in hazard ratios (HR), which is the likelihood of a patient from one group having an adverse outcome compared to a patient in the other group. A Cox proportional-hazards model was used to make sure these results were controlled for the patient's diabetes status (such that a patient with diabetes would not be compared to one without).



The primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (HR 0.82[0.73-0.92], P<0.001). The dapagliflozin group had a lower risk of worsening heart failure (HR 0.79 [0.69-0.91]), as well as cardiovascular death (HR 0.88 [0.74-1.05]). The main outcome was seen in the overall population (HR 0.77 [0.67-0.89]) as well as patients with EF <60% (HR 0.77 [0.65-0.90]). The death from any cause was not significantly different (HR 0.94 [0.83-1.07). Symptom burden was lower in the dapagliflozin group than in the placebo group (2.4 pts; [1.5-3.4]). Safety endpoints were not different in Dapagliflozin vs placebo groups.

In summary, the DELIVER study demonstrated a lower risk of CV events with dapagliflozin, consistently among subgroups of EF>60% vs <60%, DM vs non-DM, and the presence or absence of a previous left ventricular ejection fraction of 40% or less that improved to >40% by the time of enrollment. The results of this study are consistent with the results of the EMPEROR-Preserved trial though the latter demonstrated attenuation of the Empagliflozin effect in patients with the highest range of EF. Some limitations of this study include strict inclusion criteria and subsequently restricted generalizability, a small number of African Americans, and the inability to perform symptom burden assessment of some patients due to COVID-19 restrictions.

DO THE OMICRON MULTI-VACCINES WORK?

Article by John West (PGY1)

With novel COVID variants continuing to arise, particularly for highly mutagenic strains like Omicron, there is concern for reduced efficacy of currently available vaccines. A recent study (Chalkias et al. NEJM 2022) sponsored by Moderna hopes to demonstrate the safety of Moderna's bivalent COVID vaccine and its efficacy against both ancestral variants and the newer Omicron variant. The study is currently ongoing, with interim results reported from phase 2-3.

To meet inclusion criteria, participants had to complete a two dose primary series of the Moderna vaccine along with one Moderna booster at least 3 months prior to enrolling. Participants who had known COVID infection within 3 months prior to screening were excluded. There were 819 participants enrolled, and a total of 437 received the bivalent booster and 377 received the monovalent booster. The study was open label. Both demographic groups were comparable, with a mean age of 57, 50-59% female, predominantly white (85-87%), with 22-27% having prior known COVID infection.

The primary immunogenicity measurement was the neutralizing antibody response against Omicron strains and ancestral SARS-CoV-2 with the D614G mutation. The goal was to demonstrate that the antibody response generated from the bivalent booster was superior or noninferior compared to the monovalent booster. After adjustment for age groups and pre-booster titers, the geometric mean titer ratios (bivalent titer divided by monovalent titers) were 1.22 (97.5% CI, 1.08 to 1.37) for ancestral variants and 1.75 (97.5% CI, 1.49 to 2.04) for Omicron strains, meeting the prespecified criteria of Omicron superiority and ancestral non-inferiority. Safety criteria in this study included local and systemic adverse reactions within the first 7 days, unsolicited adverse events within 28 days, and severe adverse events throughout the entire study period (approximately 12 months). Similar safety profiles were shown between the two boosters with localized pain, headache, and fatigue being most reported. There were no serious adverse events related to vaccination in either subgroup.

Based on the reported findings, there is encouraging data regarding the efficacy of the Moderna bivalent vaccine against the Omicron variant. It demonstrated superior immunogenicity against omicron compared to the monovalent *without* compromising immunogenicity against ancestral strains while also demonstrating comparable safety profiles. This is promising for future COVID vaccines should new strains continue to arise, because it demonstrates that **multivalent vaccines** can protect against new strains of concern without decreased immunogenicity against previously circulating strains.

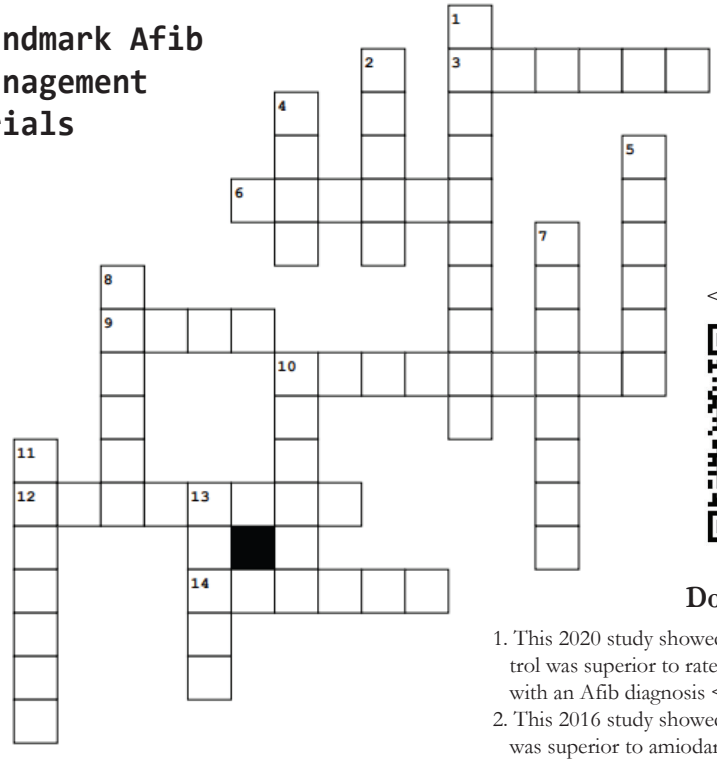
However, the study does have its limitations such as being open-label predisposing to bias and having a largely white participant demographic (>80%) limiting generalizability. Also, given both the seroresponse and immunogenicity data only being obtained at 28 days, there is uncertainty surrounding the duration of the effects of the booster vaccines. As this is an ongoing study, we will learn more about the long term efficacy of the bivalent boosters when studies are concluded. Both the Moderna and Pfizer bivalent vaccines have been authorized for **emergency use** by the FDA as of August 31st.

CROSSWORD PUZZLE

Please send your answers to
tott.midtown@gmail.com
Answers available on the next edition!

Congrats to Priyanka and Danyal for the correct answers from last edition!

Landmark Afib Management Trials



<Answers- Sept '22>

Across

3. This 2002 trial showed that rate control is equivalent to rhythm control in terms of outcomes while lower in adverse event incidence.
6. This 2019 study showed that catheter ablation did not show significant reduction in CV events compared to medical treatment
9. This 2009 trial showed that dabigatran is an acceptable alternative to warfarin for stroke prevention in Afib
10. This 2011 trial showed that apixaban was a superior and safer alternative to warfarin for stroke prevention in Afib
12. This 2011 trial showed that apixaban was superior to aspirin for stroke and systemic embolism prevention
14. This 2001 study explored the predictive value of an Afib classification scheme that we still use today.

Down

1. This 2020 study showed that early rhythm control was superior to rate control for patients with an Afib diagnosis <1 year
2. This 2016 study showed that catheter ablation was superior to amiodarone among patients with AFib and HFrEF
4. This 1991 trial showed that warfarin and ASA was superior to placebo for stroke prevention
5. This 2009 trial showed that DAPT can be an alternative to warfarin for stroke prevention
7. This 2018 study showed that catheter ablation reduced death among patients with AFib AND heart failure
8. This 2015 study showed that periprocedural bridging for anticoagulation increased bleeding
10. This 2009 study showed that dronedarone reduced hospitalization and death in Afib
11. This 2010 study explored the predictive value of a popular bleeding risk evaluation tool
13. This 2011 trial showed that a resting HR goal of 110 is equivalent in outcomes compared to stricter goals.

CLASSICAL TRIAL REVIEW

ACURASYS:
Neuromuscular Blockade for Severe ARDS

Articles by Gajendra Chaudhry (PGY1)

There are conflicting results in the literature about the possible role of Neuromuscular Blockade (NMB) before starting mechanical ventilation in ARDS patients. Some studies showed improvement in these patients' short- and long-term mortality rates, and some suggested that the possible adverse effects of NMB, like ICU-acquired weakness and cardiovascular adverse events, outweigh their benefits. The **ACURASYS,** published in 2010, was the first clinical trial that investigated the possible beneficial role of NMB in these scenarios.

The ACURASYS was a multicenter clinical trial comparing the effects of cisatracurium besylate (a neuromuscular blocking agent) versus the placebo in adult patients diagnosed with acute and severe ARDS. The trial included 340 patients from 20 different intensive care units across France, out of which 178 patients were enrolled in the "treatment" arm, who received cisatracurium besylate over 48 hours, and 162 patients in the "control" arm, who received a placebo over the same period. Regarding the trial's outcome, the mortality at 28 and 90 days after enrollment and the requirement for ICU-acquired paresis between the two arms were compared.

This study showed that (1) the 28-day mortality rate in the "treatment" arm (24% [18% - 31%]) was lower than the "control" arm (33% [27% - 41%]), though this difference was not statistically significant (p-value = 0.05), (2) the risk of 90-day mortality in the "treatment" arm (hazard ratio of 0.7 [0.5 – 1.0], p-value = 0.04) was significantly lower than the "control" arm, after accounting for the effects of possible confounders (measures of disease severity at baseline), and (3) there was no significant difference between in the rate of ICU-acquired paresis in the arms of the trail.

The results of the ACURASYS trial were widely accepted as the basis for endorsing the use of NMB in ARDS patients before starting mechanical ventilation until 2019 when the results of the ROSE trial were published in the New England Journal of Medicine. The ROSE trail included a larger population of patients (1,006 versus 340) and had broader inclusion criteria (moderate-to-severe versus severe) to investigate the same question as the ACURASYS. However, the ROSE trial failed to show any benefits of using NMB in ARDS patients in improving the 90-day mortality rate.

Although there are some arguments that the results of the ROSE trial were confounded by the differences between the two arms of their study, the current consensus for using NMB in ARDS patients is to have an individualized approach. Recent trials and meta-analyses suggest limiting the use of NMB in ARDS patients before starting mechanical ventilation to patients with refractory hypoxemia, patient-ventilator dyssynchrony, and those with a high risk of barotrauma.

OLD vs NEW Trials

AFFIRM vs EAST-AFNET4

-from rhythm control to rate control, now back to rhythm control

Article by Mohamed Iesar Abdelaziz Mohamed (PGY1)
Edits by Jeayoung Park (PGY3)

As recent as the 1990s, the overwhelming school of thought for non-valvular atrial fibrillation (Afib) management centered around rhythm control, as it would theoretically induce fewer symptoms, decrease the likelihood of stroke, enable patients to discontinue anticoagulation, and lead to overall improved survival.

The AFFIRM trial (2002) was one of the landmark trials that supported the use of rate control medications as first-line agents instead. It was a large trial with a total of 4060 enrolled patients of age >65 undergoing simultaneous treatment at 213 centers. Some subjective criteria to patient recruitment were used—patients' atrial fibrillation had to be deemed likely to recur, likely to cause illness or death, likely warrant treatment (based on clinical judgment), or carry other risk factors for stroke or death.

The rate control arm used one or more agents to control the ventricular rate to <80 bpm at rest and <110 bpm after exercise. Anticoagulation was mandated in this arm unless otherwise specified. As for the rhythm control arm, patients were treated with an antiarrhythmic (Class Ia, Ic and III) at the discretion of the treating physician. At times, cardioversion was used as necessary. Anticoagulation with warfarin was strongly encouraged but not mandated. If either chemical or electrical cardioversion failed, ablation or maze procedures were performed.

Patients were followed up for a median of 3.5 years and analysis was conducted in an intention-to-treat manner. The 5-year all-cause mortality (primary endpoint) was not significantly different between the two groups. (HR 1.15; 95% CI 0.99-1.34, p=0.08). The secondary composite outcome combining death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and etc. was similar between the two groups. There was a difference, however, in hospitalizations and adverse drug events, which was more frequent in the rhythm control gorup. Rhythm control also seemed to increase (although not significantly p=0.07) the overall mortality risk in those with a normal LVEF, those with established CAD, and patients over 65.

The AFFIRM trial concluded that the benefits of rate control and rhythm control were equivalent, and rate control should be preferred as there were less adverse events. The trial had major limitations however—because anticoagulation was not mandated in the rhythm control arm, adverse events occurred frequently amongst patients whose anticoagulation was withdrawn. The study was also criticized for the subjective nature of patient selection, relying heavily on clinical judgment. Patients with severe symptoms were frequently excluded by the recruiters from the rate-control arm and that might have skewed the results in its favor. A lack of generalizability for the younger population, especially those with no risk factors for ASCVD or CVD, was noted as well.

Despite these lingering questions, rate control continued to be the first-line therapy for non-valvular Afib for the next two decades. The field has changed since then, however—ablation techniques became more available and sophisticated, warfarin became gradually phased out by other anticoagulants, and new effective rhythm control drugs such as dronedarone came into the picture.

With these new developments in mind, the **EAST-AFNET4 trial** was conceived in 2013 to revisit the same question. Much like the AFFIRM trial, it was a large-scale (n=2789) open-label trial only blinded to outcome assessment, but the study focused on patients whose atrial fibrillation was newly diagnosed (median days since diagnosis was only 36 days). In addition, 8% of the rhythm control group patients were initially treated with ablation (20% received ablation by 5 years), unlike in the AFFIRM trial where ablation was considered a last-resort strategy. The rate control group ("usual care" group) limited the use of rhythm control only for the management of symptoms. The first primary outcome was a composite of death, stroke, or serious adverse events, while the second primary outcome was the number of hospital nights spent in a year.

The study showed that the early rhythm control strategy was superior in regards to the incidence of primary outcome events (3.9% vs 5.0%, incident ratio 0.79, 96% CI 0.66-0.94). Individual components such as death from CV causes (incident ratio 0.72 [0.52-0.98]), stroke (0.65 [0.44-0.97]), hospitalization from heart failure (0.81 [0.62-1.02]), hospitalization from acute coronary syndrome (0.83 [0.58-1.19]) were consistently in favor of rhythm control. The second primary outcome, the nights spent in the hospital per year, were not significantly different (5.8 vs 5.1, ratio 1.08, 99% CI 0.92-1.28). Most other secondary outcomes such as ejection fraction, symptoms scores, and cognitive scores, as well as safety outcomes, did not show a significant difference. Further pre-specified sub-analysis showed that the clinical benefit of early rhythm control was consistent between patients with or without heart failure, as well as symptomatic and asymptomatic patients. Most importantly, the presence of sinus rhythm at 12 months explained 81% of the treatment effect based on causal mediation analysis.

<ToTT newsletter>
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Thank you to our readers, it has been a wonderful year.
Sincerely,
ToTT team

Limitations of the trial include the non-blinded nature of the study design as well as the relatively high number of patients lost to follow-up (9.0% in the rhythm group, 6.6% in the usual care group). The efficacy of different rhythm control strategies was also not compared. Therefore, more sham-controlled trials focusing on individual interventions would strengthen the argument for early rhythm control. In addition, because anticoagulation was continued in both groups through the entire study, it is yet unknown what the clinical benefit would be in the absence of anticoagulation. As this debate is still unfolding, the latest AHA/ACC guidelines have yet to reflect these new findings.