

Welcome to Kuma's Koushik's Corner*!

*Every week Kuma usually does a quick recap of an article, but sometimes a resident steps in and teaches him a thing or two. If you have any suggestions for a paper, or want to join his weekly newsletter for residents that does more in depth dives into papers, let him know. For this week's breakdown—

[Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. Isabelle Van Gelder. Van den Berg MD. \(RACE II Trial\). NEJM. April 2010.](#)

Why? Cardiology guidelines previously recommended strict rate control targets for AFib, but these were generally empiric and not particularly evidence-based. The idea was that strict rate control would improve symptoms and reduce the risk of heart failure, but strict control also comes with a higher risk of side effects with more meds at higher doses. The first RACE Trial showed that rate control was non-inferior to rhythm control in AFib, so the RACE II Trial tested if lenient rate control is non-inferior to strict rate control in preventing cardiovascular events.

Who? Adults with permanent atrial fibrillation (for up to 12 months), aged 80 years or younger, with mean resting HR above 80 beats per minute, without a history of stroke, and currently on anticoagulation or ASA (if no indication for AC).

How? Randomized, prospective, multi-center, open-label, non-inferiority study that compared lenient rate control (HR < 110 at rest) with strict rate control (HR < 80 at rest, < 110 with exercise). Patients recruited from January 2005 to June 2007 at 33 centers in the Netherlands (follow-up ended June 2009). Patients received dromotropic drugs (beta-blockers, non-dihydropyridine CCB's, or digoxin) alone or in combination to achieve the HR goal. Patients followed up every 2 weeks until HR goal met, and then at 1, 2, and 3 years.

What was measured? Primary endpoint was a composite of death from cardiovascular causes, hospitalization for HF, stroke, systemic embolism, major bleeding, and arrhythmic events (syncope and sustained VT, cardiac arrest, life-threatening medication side effects requiring hospitalization, and pacemaker/ICD implantation for bradycardia/sustained VT).

What happened? Final study size was 614 patients (n=311 in lenient group, n=303 in strict group). Total cohort was 66% male with average age of 68, median duration of Afib of 18 months, and average resting HR of 96. 10% of patients had a previous HF hospitalization. Strict group had a higher percentage of fatigue, palpitations, and dyspnea.

98% of the lenient group and 67% of the strict group met their HR goal. Mean HR at 1, 2, and 3-year follow-up were 86, 84, and 85 in the lenient group vs. 75, 75, and 76 in the strict group (p<0.001). 3-year cumulative incidence of the primary outcome was 12.9% in the lenient group and 14.9% in the strict group, with an adjusted HR of 0.8 (0.55-1.17). Overall, the lenient group was non-inferior to the strict group for the primary and secondary outcomes by pre-specified study margins.

But But? The study was powered for a 10% non-inferiority margin in the primary outcome between the lenient and strict groups, and had to increase recruitment due to lower rates of the outcome than expected in each group. There was also a pretty notable difference in how often the HR goal was met between the two groups (98% in lenient vs. 67% in strict, and 78% of patients in the lenient group had a HR < 100). So was there really that significant of a difference between the two groups? Can most patients even tolerate strict control? Additionally, the HR CI for the primary outcome was 0.5-1.2, which could be considered fairly wide (lenient group either 50% better or 20% worse than strict group).

So What? Overall, this trial made quite an impact when it was published in 2010 and was included in the ACC guidelines that suggested prioritizing lenient rate control over strict rate control for most Afib patients. But its findings may have been limited by a smaller-than-expected difference in heart rates between the two groups and a fairly low number of patients with HF included in the study. However, 15 years later and this data appears to have held up. It is another situation where giving patients less medication is a good thing, and that seems to be true for AFib strict rate control as well.

Welcome to Kuma's Jinal's Corner*!

*Every week Kuma usually does a quick recap of an article, but sometimes a resident steps in and teaches him a thing or two. If you have any suggestions for a paper, or want to join his weekly newsletter for residents that does more in depth dives into papers, let him know. For this week's breakdown—

[Safety and efficacy of rilzabrutinib vs placebo in adults with immune thrombocytopenia: LUNA3 study. David J. Kuter. Amed Daak. Blood. June 2025.](#)

Why? Current treatment for ITP has a high relapse rate, long term side effects, and/or fails to mitigate the fatigue associated with ITP. Rilzabrutinib is a highly selective and specific Bruton Tyrosine Kinase Inhibitor that has shown efficacy in phase 1-2 trials in patients with difficult to treat ITP

Who? Adults with chronic, persistent ITP that had 2 readings of platelet counts <30 and no single reading >35 in the screening period who had been treated previously with other therapies including IVIG, corticosteroids, TPO-RA, Rituximab.

How? Randomized, placebo-controlled, double blind trial that evaluated efficacy + safety of Rilzabrutinib in patients with chronic, persistent ITP. In 2:1 ratio, received either Rilzabrutinib 400 mg BID or placebo for 24 weeks. 2:1 randomization was used to allow for more safety data to be collected. At 12 weeks, platelets

counts measured and platelet responders (defined as plt count >50 and at least doubling from baseline) could continue through week 24. At week 24, plt counts measured again.

What was measured? Primary end point was sustained platelet response — defined as >50 for 2/3 or more of the 8 weekly scheduled plt measurement sessions during the last 12 weeks. At least 2 of these counts had to be in the last 6 week of the 24 week trial. Secondary endpoints include number of weeks with plt count >50 and at least doubling from baseline. Secondary endpoints included need for ITP rescue therapy and healthcare-related quality of life (HRQOL).

What happened? 202 participants total, 69 received placebo and 133 received Rilzabrutinib. Average age 47, 63% women, and 46% of this group had greater than 5 prior ITP therapies with average duration of disease 7.7 years.

Primary end point was met in 23% of those who received Rilzabrutinib vs 0% of those on the placebo pill (p-value < 0.0001). Rilzabrutinib also reduced need for ITP rescue therapy by 52% and improved HRQOL including physical fatigue. However, there was only an improvement of 8 on the fatigue scale, which is technically less than the minimal clinically significant difference (>10).

But But? The study had a quirk where if there was no response at 12 weeks the patients were taken out of the study--only 10 patients in the placebo group completed the full 24 weeks vs 69 in the Rilzabrutinib group.

Rilzabrutinib is associated with higher rates of diarrhea than the placebo (23% vs 4%). Other commonly experienced side effects include nausea (17%) and headache (8%). However, most of these adverse events (AE) were grade 1 or 2. 6 % of Rilzabrutinib group discontinued due to therapy vs 0% in placebo arm.

So What? This study demonstrates that Rilzabrutinib is effective for treatment of ITP in adult patients with chronic, persistent ITP, and Rilzabrutinib can be considered for treatment especially when patients have not shown a good response to other therapies. The durability of its effect is yet to be determined, and adverse events could be an issue.

Welcome to Kuma's Manvita's Corner*!

***Every week Kuma usually does a quick recap of an article, but sometimes a resident steps in and teaches him a thing or two. If you have any suggestions for a paper, or want to join his weekly newsletter for residents that does more in depth dives into papers, let him know. For this week's breakdown—**

A Randomized Trial of Intensive vs Standard Blood Pressure Control (SPRINT Trial). The Sprint Research Group. November 2015. NJEM.

WHY? – We know current hypertension guidelines define normal BP as $<120/80$, stage 1 hypertension as $130-139/80-89$ and stage 2 as $\geq 140/\geq 90$. In patients without diabetes or a history of stroke then, is there any benefit in intensive BP control to target SBP < 120 compared to standard treatment (target SBP < 140)? The SPRINT trial is a major study that looked at this.

HOW? – Multicenter, open-label, randomized control trial, intent to treat. 9361 participants without diabetes or stroke who are at elevated CV risk were enrolled across 102 sites. 4678 were randomized to the intensive target SBP < 120 arm and 4683 to the standard target SBP $135-139$ arm. Their inclusion criteria were age ≥ 50 , SBP higher than 130 on 1-4 medications, ≥ 1 CVD risk criteria (MI, PCI, CABG, CEA, revascularized PAD, AAA, etc), CKD, high ASCVD. Some of the exclusion criteria included diabetes, stroke, secondary hypertension, low LVEF.

WHAT WAS MEASURED? – The primary outcome they looked at was the occurrence of a cardiovascular event such as ACS, stroke, heart failure or CV death.

WHAT HAPPENED? – Participants were treated with standard antihypertensives (thiazides, ARBs, CCB were the most common to achieve their goal SBP and followed up monthly for the first 3 months and then every 3 months after that. In the first year the intensive treatment group had mean SBP 121.4 and the standard treatment group had mean SBP of 136.2. Participants in the standard treatment arm had SBPs targeted to 135-139 and if they dropped below 130 their medications were decreased.

Overall, 562 participants had a primary outcome event, with 243 being in the intensive treatment group and 319 in the standard treatment group ($P < 0.001$). This calculated out to a number needed to treat of 61 (good impressive!) Adverse events like hypotension, syncope, electrolyte abnormalities occurred more frequently in the treatment arm. Specifically AKI leading to an ED visit events happened in 204 intensive treatment group participants and 120 standard treatment group participants ($P < 0.001$). This calculates out to a number needed to harm of 50 (bad impressive!). But the main headline was the study was stopped early because of the benefit. In fact, even all-cause mortality was better in the intensive treatment, with a number needed to treat over 3 years of 100.

BUT BUT? – When studies are cut short like this I always wonder if there's some overestimation of the benefit of intervention. Another thing to consider is that the control arm isn't standard of care (we don't usually stop/decrease medications just because someone's SBP < 130), so that makes it a little hard to assess things. And the adverse events are not benign, but then again, AKI is bad, but being dead is worse.

SO WHAT? – In patients who don't have a history of DM or stroke, but have elevated CV risk, more intensive BP control aiming for SBP 120 may be beneficial in reducing rates of cardiovascular events, but it comes with the risk of those adverse events too.

Welcome Back to Cunningham's Corner! *Guest Edition*

***Every week Dr. Folmsbee does a quick recap of a random article, but sometimes residents take over! If you have any suggestions for a paper or want to join the weekly email he sends to residents that does a more in-depth dive, let him know. For this week's breakdown–**

Pulmonary Vein Isolation vs Sham Intervention in Symptomatic Atrial Fibrillation The SHAM-PVI Randomized Clinical Trial

WHAT? – Pulmonary vein isolation (PVI) has been used as a cornerstone of symptomatic AFib treatment. While previous studies such as the CABANA trial have studied PVI in an observational manner and suggested improvement in symptoms and QOL, there has never been a sham-controlled trial. This is surprising given US and European guidelines list PVI as a class 1 recommendation for symptomatic AFib. In the absence of randomization, it is difficult to tease out the influence of a placebo effect. This study sought to more clearly objectively measure efficacy of PVI. Does it really work or is the benefit explained by a placebo effect?

HOW? - Double-blind RCT of PVI vs. sham procedure in patients with symptomatic atrial fibrillation. All antiarrhythmics were stopped before the procedure to isolate the placebo effect

WHO? - 126 patients with symptomatic AFib (pAF or persistent) enrolled at 2 tertiary care centers in the UK. Mean age 67, 70% male.

WHAT WAS MEASURED? – Atrial fibrillation burden 6-months following randomization compared to baseline as measured by an implantable loop recorder. Secondary outcomes included patient reported QOL measures, times to event, and safety events.

WHAT HAPPENED? – 64 patients underwent cryoablation PVI and 62 underwent a sham procedure of phrenic nerve pacing. All patients in AFib at the time of randomization underwent DCCV. 6-months after randomization, patients in the PVI group had a 60% reduction in AFib burden as compared to 35% of patient in the sham group (mean difference 0.25, 95% CI 0.15 to 0.42, $p < 0.001$). In other words, a 75% reduction in AF burden at 6-months for PVI as compared to the sham.

SO WHAT? - They were not your average Afib patient. To get into the study the patients had to have had afib for at least two years and basically fail medication management. It is also not standard to stop medications before ablation but in this case the authors were trying to isolate the placebo effect which is good but does limit generalizability.

BUT BUT: The length of follow-up in this study is limited to 6-months. As implied by the CHADSVASC risk scoring system, many of the risks of AFib are incurred on a longer time scale. The questions of whether the benefit of PVI is durable and, importantly, whether this correlates with a change in outcomes such as stroke or HF remain unanswered.

ONE LAST THING: In this study, it is interesting to think about the ethical principle of equipoise ~ how certain are you that the answer to your research question is in doubt? Ablation has been around for nearly 20 years, why did it take so long to do this study? How much should we trust observational studies? Imagine if this study was negative? It would have been a disaster for the field as that might mean we had been doing ablations for years without any benefit (and only harm). On the other hand, there is no RCT for the parachute when skydiving. Medicine must balance that with the potential harm in forging ahead with blind faith with ineffective/unproven therapies.