May 2022 Special **Graduation** Issue

# *Talk of the Town*

-A Midtown Journal Club Newsletter


## MASTER-DAPT:

## Abbreviated Antiplatelets After Coronary Stenting

Article by Aleksan Kachatryan (PGY1)

The optimal duration of antiplatelet therapy (APT), as well as the type of APT (dual-antiplatelet (DAPT) versus single antiplatelet therapy (SAPT)) after coronary stenting remains unclear. This is often further complicated by co-morbid conditions with an indication for oral anticoagulants (OACs).

Previous trials such as the GLOBAL LEADERS trial (**Vranckx** et al., *Lancet* 2018) and STOPDAPT-2 trial (**Watanabe** et al., *JAMA* 2019) investigated this topic in the low bleeding risk population, but evidence in the high bleeding risk population is yet lacking.

The recent **MASTER DAPT** trial tested the outcomes of abbreviated versus non-abbreviated APT treatment in the high-bleeding risk (age >75, recent bleeding episode, history of stroke, use of anticoagulants, steroids, or NSAIDs) population. In this international multi-center study, 4579 patients first received a biodegradeable-polymer sirolimus-eluting (Ultimaster) stent. After 1 month of DAPT, patients were randomized to either **abbreviated** (1 months DAPT then 5 months of SAPT, or if on OAC, 6 months of SAPT) or **non-abbreviated** APT strategies (6 months DAPT, or if on OAC, 3 months of DAPT).

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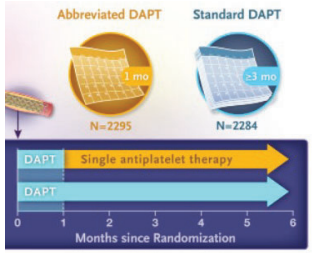
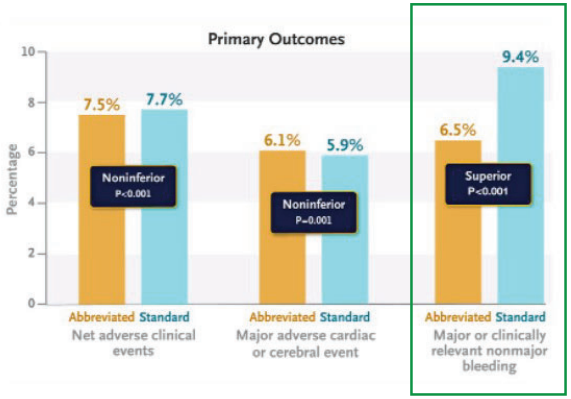
Exclusion criteria were implantation of a stent other than Ultimaster within the previous 6 months, or implantation of a bioresorbable scaffold at any time before the index procedure. Patients undergoing treatment because of in-stent restenosis or stent thrombosis were also excluded.




Co-primary outcomes were 1) net adverse clinical outcomes, defined as the composite of all-cause death, myocardial infarction, stroke, and bleeding event, 2) major adverse cardiac and cerebral events, expressed as a composite of all-cause death, myocardial infarction, and stroke, and 3) major or clinically relevant nonmajor bleeding, defined as a composite of Bleeding Academic Research Consortium (BARC) class 2 (nonmajor but clinically overt), 3 (non-cardiac with Hgb drop <5g/ml or neurologic), and 5 (fatal) bleeding events (Mehran et al. Circulation 2011). BARC class 4 (CABG-related bleeding) was excluded.

In both per-protocol and intention-to-treat populations, there were no significant differencesbetween abbreviated DAPT and standard DAPT groups for net adverse clinical events (hazard ratio (HR) 0.94 [0.76, 1.15]) and major adverse cardiac and cerebral events (HR 0.99 [0.78, 1.26]). On the other hand, the rate of major or nonmajor clinically relevant bleeding was significantly lower in the abbreviated DAPT group (HR 0.68 [0.55, 0.84]; abs risk difference (RD) -2.82% [-4.40, -1.24])




This difference in bleeding rates was mainly due to the population **without** pre-existing clinical indications for 12 months of OAC—(RD -3.52% [-5.29, -1.74]). In patients with clinical indications for OAC, a difference in bleeding rate was not seen (RD -1.75% [-4.75, 1.25]).

**In short,** among patients at high risk for bleeding who had undergone drug-eluting stent placement, the discontinuation of DAPT at a median of 34 days after PCI was noninferior to the continuation of DAPT for a median duration of 193 days for net adverse clinical events and major adverse cardiac and cerebral events and was **superior** in terms of bleeding.

An important limitation of the study is that this was a very heterogeneous group of patients with differing number, type, or location of coronary lesions, receiving a heterogeneous group of medications (the choice of P2Y12 inhibitor or ASA for SAPT was at the discretion of each provider). The trial was also open-label, but practically it would have been impossible to mask three oral P2Y12 inhibitors and aspirin. The results of this trial might not be applicable to patient who received other types of stents. Overall it appears important to assess the bleeding risk of patients undergoing stent placement to strategize what antiplatelet therapy is best.

# Is Serial Lactate *Superstition*?

## A Review of **LACTATE (2010)** & **ANDROMEDA-SHOCK (2019)**

Article by Siham Hussien (PGY1), Jeayoung Park (PGY2)

Since its discovery in 1834 by Scherer et al. in the bloodstream of patients in shock, lactate levels have been accepted as a key prognostic marker for patinets with sepsis. It has become one of the most frequently ordered labwork ordered for patients admitted to the hospital. However, even until today, the evidence for obtaining **serial** lactate for management of sepsis is debated.

The landmark **LACTATE** trial (Jansen et al. *AJRCCM* 2010) is one study that investigated the role of serial lactate in the ICU setting. Set in the Netherlands, this multi-centered open-label RCT recruited 348 adult patients with a lactate level higher than 3.0 mEq/L. Patients with an evident aerobic cause of hyperlactatemia (i.e., type B lactic acidosis), liver failure , liver surgery, epileptic seizures (grand mal, shortly before or during admission), or DNR status were excluded. Both intervention ("lactate group") and control groups received goal-directed medical therapy in terms of blood pressure, heart rate, etc., but the lactate group had an additional protocol of serial lactate draws every 2 hours for the first 8 hours as well as therapeutic interventions (e.g. fluid resuscitation) to decrease lactate levels by at least 20% between serial measurements. Patients' central venous oxygen saturation (ScvO2) was also measured (only in the intervention group), and those who did not achieve goal ScvO2 received **vasodilators** such as nitroglycerin.

Analysis showed that when adjusted for age, sex, APACHE II socre and SOFA score, the lactate group had a significantly **lower** in-hospital mortality ratio of 0.61 (95% CI 0.43-0.87) and also was more likely to be discharged from the ICU earliler (HR 0.65, 95% CI 0.50-0.85). Rate of organ failure (based on SOFA score) was lower in the lactate group as well (but p=0.27).

Surprisingly, **both groups lead to similar rates of lactate reduction** (at 8 hrs: 2.7 vs 2.6, p=0.59; at 72 hrs: 1.7 vs 1.6, p=0.17). Both groups received similar amounts of vasopressors, but the lactate group received significantly less fluids (2.1±1.7L vs 2.7±2.0L, p=0.01) compared to the control group. The lactate group did receive more vasodilators as per research protocol--if ScvO2 was greater than 70% but the lactate level did not decrease more than 20%, vasodilator therapy was given to improve microvascular perfusion. This may have complicated results.

Overall, lactate levels may have served as a "**warning sign**" for providers to adjust and adapt their treatment strategies accordingly, rather than a ture marker of improvement in patient's clinical status. But if that were the case, couldn't *any marker of peripheral perfusion* be a useful clinical sign for septic patients?

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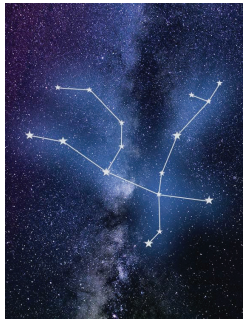
The **ANDROMEDA-SHOCK** trial (Hernandez et al., *JAMA* 2019) investigated the potnetial of monitoring other markers of peripheral perfusion, such as **capillary refill** time, in order to assist resuscitation efforts. This study was conducted in 28 hospitals in 5 South and Central American countries and was designed as an open-labeled superiority trial. Patients with early septic shock (<4 hours since onset) admitted to the ICU were included, and patients with anticipated surgery, dialysis, or DNR status were excluded. The study compared **peripheral perfusion**-targeted resuscitation, in which capillary refill time was measured every 30 minutes, against **lactate level-**targeted resuscitation where labs were drawn every 2 hours for 8 hours (the same as the LACTATE trial). If treatment goals were not met, both groups applied the same protocol (fluids, vasopressors, then inodilators) to guide further management.



Results showed that 28-day mortality was actually **lower** in the capillary refill time (CRT) group compared to the lactate group (hazard ratio 0.75, [0.55-1.02], p=0.06). The CRT group also had lower lactate levels at 48 and 72 hours, and overall used less fluid and vasopressors to optimize therapy. There was no significant differnece in ICU length of stay or mechanical ventilation free days. Although the study had very good standardized protocols and good adherence, it was underpowered in temrs of sample size (i.e. p= 0.06 despite a 8.5% absolute mortality difference). Also, while the CRT group was allowed to reassess and adjust the treatment strategy every 30 mintues, the lactate group was only allowed to do so every 2 hours-- which could have biased the results against the lactate group. It would also have been informative to assess a combined CRT+lactate approach. Nonetheless, it appears that whichever method is used, the important part is the **frequent reassessment** of the patient's clinical status rather than the type of monitoring itself.

**In this special issue, we proudly present....**

# Resident Research!

## Nitrogen Balance as a Marker of Proper Nutrition for ICU Survivors

Research by Dena Tran (PGY3)

Survivors of critical illness requiring prolonged mechanical ventilation (PMV) are predisposed to malnutrition, muscle wasting, and weakness. There is limited data regarding proper nutrition among these patients, and although nitrogen balance has been studied as a marker of adequate protein intake in healthy individuals, it has not been well studied in critically ill PMV patients.

We performed a retrospective, cohort study design (n = 16), patients requiring PMV at our long-term acute care hospital (LTACH) at the University of Maryland Medical Center Midtown Campus. Patients included in this study were defined as survivors of critical illness receiving PMV in a LTACH who had a random 24-h urine collection for urea nitrogen (24hrUUN). Energy and protein intake was calcul-

ated from chart documentation of dietary intake for the 24-hour period. Nitrogen intake was estimated from protein intake. Dietary intake was compared to RD-recommendations to determine the percentage of RD-recommendations achieved.

Patients had a mean age of 61.5 ± 3.2 years and mean BMI of 27.5 ± 2.5 kg/m2. Duration of LTACH hospitalization was 26.5 (6-221) days. Mean energy and protein intake was 21.7 ± 2.9 kcal/kg/d and 1.1 ± 0.1 g/kg/d, respectively, which corresponded to 86% of both RD energy and protein recommendations. Ten patients achieved a positive nitrogen balance (mean 0.9 ± 1.1 g). In addition, there was a positive linear relationship between protein intake and nitrogen balance ($r = 0.59$, $p = 0.016$). Overall, survivors of critical illness requiring PMV achieved a high percentage of RD-recommended protein and calories, and prevented a negative nitrogen balance in a majority of patients.

## Identifying *Novel* Genetic Variants with Increased Risk of CV Disease

Research by Fahad Alkhalfan (PGY2)
& Alex Gyftopoulos (PGY3)

Recent studies have demonstrated that traditional risk factors such as diabetes, hyperlipidemia, hypertension, and smoking may only account for a small proportion of variance in atherosclerosis, suggesting that there may be novel nontraditional and genetic risk factors that have yet to be identified.

We analyzed the UK Biobank, which is a large long-term biobank study that contains clinical and genetic data gathered from over 500,000 individuals in the United Kingdom who were between the ages of 40 and 69 at the time of recruitment. In this genome wide association study, we used Plink's GLM options to analyze associations between genotypes and phenotypic manifestations of the disease. We identified 189 variants in 8 different genes with $p<0.0001$ with minor allele frequency >0.5% in 9,726 and 6,699 instances of cerebrovascular disease as a primary or secondary diagnosis. Four groups of variants were identified in close proximity to sequences for the following genes: PITX2, LPA, LRRTM4 and CDKN2B-AS1. These genes are known to be associated with cardiovascular conditions such as Afib and atherosclerosis. Further studies are warranted to confirm this analysis and its applicability in improving CVD risk stratification.

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## *Racial and Ethnic Disparities in Diabetes Technology Use among Adults with Type 1 DM*

Research by Jeayoung Park (PGY2)
Yazan Alzedaneen (PGY2)
& Khulood Bukhari (PGY3)

Despite recent advances in diabetes technology, the distribution of healthcare resources are often unequal among racial and socioeconomic groups. We reviewed the charts of all adults with T1DM who attended the University of Maryland Center for Diabetes and Endocrinology (UMCDE) between 1/2019 and 12/2019. Age, gender, race/ethnicity, type of insurance, ZIP code, BMI, A1c, method of insulin delivery, and type of glucose monitoring device were obtained from each chart We utilized the 2019 US Census data to determine the median income for each ZIP code.

A total of 532 adults were included in the study; 277 identified as non-Hispanic (NH) White, 204 identified as NH Black, 7 identified as Hispanic, and 44 identified as other racial/ethnic groups. NH White adults had a significantly higher insulin pump use when compared to NH Black (54% vs 17%, OR 2.76 after regression, 95%CI [1.62-4.71]). Similarly, NH White adults had significantly higher continuous glucose monitor use when compared to NH Black (66% vs 34%, OR 1.95 after regression, 95%CI [1.23-3.07]). Insurance type was an important effect modifier for the use of insulin pump between NH White and NH Blacks (Pooled OR 3.14 [2.0-4.9], Medicare OR 13.5, Commercial Insurance 2.7, Medicaid 2.2). Overall, NH White adults with T1D were significantly more likely to have been prescribed diabetes-related technologies when compared to other racial/ethnic groups. Future directions include a prospective study following the 2019 cohort through subsequent years to determine if any changes in technology use have occurred and to gain a better understanding of factors beyond socioeconomic status.

## IN-DEPTH REVIEW

# MODIGLIANI—
# the ultimate PE protocol?

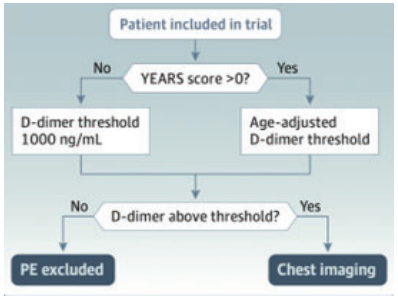
Article by Elvina Yunasan (PGY1)
& Jeayoung Park (PGY2)

Diagnosis of pulmonary embolism (PE) remains a challenge for physicians. To reduce unnecessary chest imaging, physicians often use D-dimer levels, scoring systems such as the Wells Score and GENEVA Score, or a combination of both approaches such as the YEARS algorithm. Head-to-head comparisons of these methods can often be confusing, as it would be comparing apples to oranges (**Korevaar et al.**, *Critical Care Medicine* 2020). Instead, learning how to combine some of these methods may lead to better outcomes.

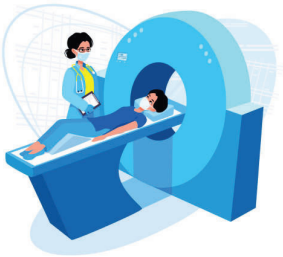
The YEARS algorithm (**ver der Hulle et al.**, *Lancet* 2017) borrows three criteria from the Wells Score and suggests a different D-dimer threshold depending on how many of the criteria are positive. The D-dimer thresholds to warrant a CT angiogram are: >1000ng/ml if none of three YEARS items are positive, versus >500ng/ml if one or more of the three YEARS items are positive. External validations of the YEARS algorithm, however, revealed a weakness in this approach—among patients with no YEARS items and a D-dimer <1000 ng/mL but still above their age-adjusted D-dimer cutoff (age X 10), PE was diagnosed in 6.3% of patients (**Eddy et al.**, *J Thromb Haemost* 2020).

This brings us to the **MODIGLIANI** trial published by Freund et al in 2021. In this trial, the YEARS algorithm was modified to use the age-adjusted D-dimer cutoff if there are non-zero YEARS items (rather than 500ng/ml for all ages)—more akin to current international guidelines for D-dimer thresholds. Notably, all patients who scored a 0 with the PERC rule have been excluded. The MODIGLIANI trial assessed the non-inferiority and cost-effectiveness of this modified diagnostic strategy (MODS) that combines YEARS and age-adjusted thresholds, against the conventional age-adjusted D-dimer level only protocol, for ruling out PE in the ED. A non-inferiority trial was chosen as the authors' main point was to prove the safety of the MODS approach alongside cost-effectiveness.

A total of 1414 patients from 18 emergency departments in France and Spain were enrolled. Included patients had a low to intermediate subjective pretest probability, with 1 or more PERC scores. Excluded patients were either with very low probability (PERC score of 0, presence of other obvious causes than PE), had a high subjective probability of PE (>50%), or with symptoms of severe illnesses (respiratory distress, hypotension, oxygen sat <90%). In the end, 1271 patients were included per-protocol analysis (648 in the intervention arm, and 623 in the control arm).




The primary endpoint of this study was the *failure* of diagnosis strategy, defined as any venous thromboembolism that was diagnosed 3 months **after** the initial PE exclusion, rather than at the time of the initial ED visit. Treatment failure was seen in 1 patient in the intervention group (failure rate 0.15% [0.00, 0.86]) and 5 patients in the control group (failure rate 0.80% [0.26, 1.86]). The adjusted difference in failure rate did not cross the noninferiority margin. Secondary endpoints iincluded chest imaging ordered by physicians, ED length of stay, and hospital admission following ED visits. Most notably the number of chest imaging (CTA or V/Q scan) was lower in the intervention group (30.4% vs 40.0%; adjusted difference -8.7% [-13.8, -3.5]). Statistical significance was not reported by the authors due to a high potential of type I error due to multiple comparisons.



There were several important limitations of this study. As this was a non-inferiority trial, per-protocol (PP) analysis was chosen over intention-to-treat (ITT) to avoid favoring the non-inferiority hypothesis. However, the preference between PP and ITT is not clearly established in non-inferiority trials and PP always runs the risk of uneven dropouts (**Sanchez et al.**, Stat Med 2006). The data from the ITT population was not reported. There were a few patients with deviations from the protocol (10-30 patients) and also missing outcomes from 37 patients—it is unknown how much influence these "dropouts" would have had on the PP population. In addition, the study lacked the power to demonstrate the safety of the MODS protocol for patients with a YEARS score of 0 and D-dimer levels above the age-adjusted threshold but below 1000 (the same patient population with safety concerns raised by **Eddy et al.** in *J Thromb Haemost* 2020)—no missed PE were found in this subgroup, but the confidence interval was rather wide due to a lack of power (the bounds of the 95% CI were 0.00%-5.36%).

It is also notable that this was a cluster-randomized study; each emergency department stuck to either the MODS protocol (intervention) or the standard age-adjusted D-dimer protocol (control). This was presumably to eliminate any variability due to each provider's preference, but this may exacerbate any bias that comes from the patient population visiting each ED. The potential bias from different patient populations visiting each ED was ameliorated by a cross-over design, where each ED used both protocols (control then intervention, versus intervention then control).

Overall, in patients with low to moderate risk of PE, a combination of YEARS criteria with age-adjusted D-dimer in those positive for PERC is non-inferior compared to the age-adjusted D-dimer alone method. This strategy also seems to be able to reduce chest imaging use, preventing unnecessary radiation high cost. To use this approach in our practice, we would 1) use the PERC rule to determine whether we should obtain a D-dimer and 2) use the modified YEARS protocol to interpret the D-dimer. For those with 1 or more positive YEARS items, the cutoff for D-dimer would be age x 10.

## Congratulations Class of 2022!

May you save even more lives, spread knowledge, and discover truth!

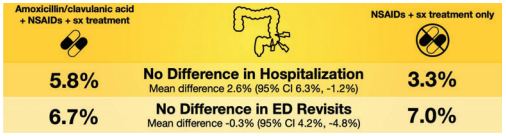
*-ToTT Staff*

# The DINAMO Study: Outpatient treatment of Mild Dirverticulitis *Without Antibiotics*

Article by Harim Kim (PGY2)

The incidence of diverticular disease is increasing. In recent years, two randomized controlled trials have shown no benefit of antibiotics in the treatment of uncomplicated acute diverticulitis (AD) in hospitalized patients. Whether outpatient treatment of AD is safe and effective was not explored well. The **DINAMO** Study (**Mora-Lopez et al.**, *Ann Surg* 2021) recruited 849 adult patients with a Modified Neff Score of 0 on abdominal CT scan and no clinical signs of sepsis. Patients with significant co-morbidities (diabetes with organ damage, recent decompensation of heart, liver, kidney disease) were excluded. The study was open label and no masking of patients or surgeons were performed.

The non-antibiotic group (treated with NSAIDs and acetaminophen only) was non-inferior to the antibiotic group (treated with amoxicillin/clavulanate + pain control) in terms of hospitalization rate (5.8 vs 3.3%, MD 2.6% [-1.17, 6.32], within noninferiority margin). Similar findings were seen with pain control and ED revisits. The study was limited by a significant number of excluded patients due to a strict selection criteria. There was also potential observer bias, as this was a open-label study where the provider knows whether they are assigned to the non-antibiotic or antibiotic group--which can influence the decision-making process of whether to admit the patient or not. Still, outpatient treatment without antibiotics appear to be a safe and effective therapeutic approach that can be considered as routine practice, offering both the economic advantages of outpatient care as well as the practical advantages of avoiding antibiotic treatment.

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