Galen (129 – 200 AD)
By Robert Thom

Galen, or Claudius Galenus, was a Greek physician and philosopher instrumental in advancing human understanding of anatomy by conducting nerve studies of live animals during dissection to identify nerve functions. He pioneered the theory that muscles were controlled by the brain via nerves.
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A 63-year-old Caucasian female in good physical health is escorted from the ICU, where her husband is in critical condition, down to the emergency room due to complaints of chest pain. She is tearful and reports worsening 9/10, substernal, non-radiating, pressure-like chest discomfort without associated symptoms. Vital signs were: temperature 35.4°C, blood pressure 162/88 mmHg, heart rate 71 beats/min, respirations 20 breaths/min, and O2 sat 98% on room air. Lab studies showed troponin I of 3.23 ng/ml (normal range 0–0.05 ng/ml) and a white blood cell count 12,000/mm3. Serum electrolytes were normal. A quick bedside echo revealed severe hypokinesis of the mid and apical segments and hyperkinetic basal walls.

You pull up her EKG:

**Describe the EKG**

Normal sinus rhythm at ~65bpm with left axis deviation, ST-segment elevations and T-wave inversions in the precordial leads most notable in V2-V3. Small T-wave inversions are also found in leads I and aVL.

**In addition to ACS, what is highest on the differential diagnosis?**

A. Digoxin toxicity  
B. Hyperkalemia  
C. Hypothermia  
D. Pericarditis  
E. Stress cardiomyopathy  
(answer on next page)
**What is the next best step in management?**

Despite high clinical suspicion for stress cardiomyopathy, you should still consult cardiology to activate the cath lab. ST elevations with elevated troponins can be seen in stress cardiomyopathy but you need to rule out obstructive coronary disease or acute plaque rupture.

Returning to the vignette, the patient is rushed to the cath lab and has remarkably clean coronary arteries. However, left ventriculogram confirms LV ballooning in the mid, distal and apical segments, with vigorous contraction of the basal segment.

**Discussion**

Stress cardiomyopathy, frequently referred to as Takotsubo cardiomyopathy (due to its resemblance to an octopus fishing pot on echo or ventriculography) or broken-heart syndrome, is a condition that mimics acute MI. It is often triggered by intense emotional or physical stress such as the death of relatives, catastrophic medical diagnoses, devastating financial losses, natural disasters, or acute medical illness including strokes. EKG changes can be indistinguishable from acute MI with similar progression of ST elevations, T-wave inversions and Q-waves. QT intervals may also prolong. Various studies have attempted to identify criteria to aid in differentiation including one recently published by Frangieh AH, et al. (2016), which noted good specificity (>95%) but poor sensitivity (as low as 12%). In addition, emotional triggers have also been associated with acute coronary syndromes and therefore, you must treat these findings as acute MI until you have angiographic evidence proving otherwise.

**References**

Risk Stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions


SUMMARY

Anti-neoplastics are among the leading causes of fatal anaphylactic reactions in the United States with taxanes leading as the most frequent causative agent. Due to the dependency on taxane therapy, desensitization protocols have emerged for the delivery of chemotherapy in the setting of potentially fatal hypersensitivity reactions. The present study sought to risk stratify patients with history of taxane hypersensitivity by both reaction severity and skin-testing into either desensitization or challenge and to identify patients who may tolerate conventional protocols on re-exposure. The study population included 164 patients with documented hypersensitivity to paclitaxel (142) and docetaxel (22) with a wide variety of malignancies including ovarian, endometrial, breast, and prostate. Nearly all (106/110) patients with history of positive or equivocal skin test to taxane were submitted initially to desensitization with 23 progressing to intermediate dosage challenge and 13 tolerating all successive regimens and resuming full-dose infusion protocol. Of the patients with negative skin testing 2 of 13 with history of severe reaction tolerated desensitization and were able to progress to challenge, the mixed cohort of prior moderate reactions and desensitization graduates yielded 22 patients of which 16 tolerated challenge; those 16 joined 5 skin test negative patients with history of mild reaction, all of which tolerated resumption of conventional protocol. The majority of patients followed tolerated re-exposure well with 89/138 without recurrent reaction and 31% with mild hypersensitivity or delayed reaction, most commonly flushing, and notably no instances of anaphylaxis. Patients with a history of atopic disease (31% of cohort) were more likely to suffer recurrent hypersensitivity reaction on re-exposure during desensitization or challenge as were those with history of gynecological malignancy.

COMMENTARY

Towards their primary endpoint the authors were successful in the resumption of full-dose infusions in 22% of the total cohort without a single episode of severe reaction; this latter point is notable as more aggressive protocols favoring rapid re-challenge have been reported with greater success rates (40-89%), however, with a 1-8% incidence of anaphylaxis on re-exposure and 2 documented cases of death in smaller cohorts. A significant proportion was not advanced from desensitization to challenge due to changes in the protocol implemented mid-study rather than inherent failure of the algorithm, ultimately affecting the reported success rate. While the present study provides data on likelihood to resume conventional infusions, in the absence of a concomitant comparison little can be meaningfully claimed towards the superiority of the current risk-stratified algorithm over prior re-challenge approaches.
Association of 30-Day Readmission Metric for Heart Failure Under the Hospital Readmissions Reduction Program With Quality of Care and Outcomes


SUMMARY
Since 2012, the Centers for Medicare and Medicaid Services (CMS) has monitored 30-day readmission rates for heart failure, myocardial infarction, and pneumonia. Each hospital has an estimated readmission rate (ERR) based on some patient baseline characteristics and case severity. Hospitals with higher than estimated readmission rates (ERR>1) face reduced reimbursements in order to incentivize hospitals to improve quality of care, theoretically leading to better outcomes and reduced cost.

This study, based out of the Cardiology Department here at UTSW, joins a growing body of literature questioning the validity of 30-day readmission rate as a valid marker of quality of care. The researchers pulled over 43,000 heart failure admission medicare claims from 2008-2011 at 171 centers participating in the Get with the Guidelines-HF registry. Centers were grouped into penalized- higher than expected readmission rate (ERR>1) and non-penalized- lower than expected readmission rate(Err<1). The ERR>1 and ERR<1 cohorts were compared for baseline patient characteristics and for quality of care metrics such as ACEi/ARB and BB for low EF-HF at discharge, anticoagulation for afib, aldosterone antagonist at discharge, etc. Finally, the cohorts were analyzed for differences in outcomes such as inpatient mortality, 1 year mortality and 1 year all-cause readmission.

Despite CMS attempting to control for baseline characteristic differences with the ERR, this study found differences in penalized hospitals vs non-penalized hospitals. The ERR>1 cohort was more likely to take care of black patients, less likely to take care of white patients, and more likely to take care of female patients (table 1). There were no differences in monitored quality care metrics between ERR>1 and ERR<1 cohorts, although the ERR<1 cohort prescribed diuretics and cardiac rehabilitation more often than the ERR>1 cohort (table 2). There was no difference in 1 year readmission rate or 1 year mortality between groups (table 3).

COMMENTARY
This study has several interesting findings. First, the estimated readmission rate, while attempting to fully control for baseline patient characteristics, is imperfect and is punishing hospitals which take care of a higher proportion of black and female patients. Hospitals which take care of a disadvantaged population (such as Parkland) will be unfairly penalized in this system. In order to mitigate these effects, it becomes increasingly imperative to document fully and accurately to
capture the complexity of the patients we take care of, thereby adjusting the case-severity index and the estimated readmission rate.

This study also found that, despite differences in 30-day readmission rate, the quality of care delivered between penalized and non-penalized hospitals did not differ in regards to quality metrics. In addition, 1 year outcomes such as death and all-cause readmission did not differ between cohorts. Interestingly, despite no statistical difference in 1 year mortality between groups, the non-penalized ERR<1 cohort had a trend towards higher 1 year mortality (31.7 vs 28.2\% p=0.07) and was more likely to discharge to home hospice (1.9 vs 1.3\% p=<0.001). This may explain some of the difference in 30-day readmission rates between facilities.

By showing no difference in quality of care or in 1 year outcomes, this study calls into question the 30-day readmission rate as a valid tool to assess hospital quality.

**UTSW Link**

**Table 1: Baseline Patient Characteristics between Hospitals (truncated)**

<table>
<thead>
<tr>
<th></th>
<th>HF-ERR ≤1</th>
<th>HF-ERR &gt;1</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>53.5 (48.5–59.5)</td>
<td>55.7 (51.6–64.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>White</td>
<td>90.3 (77.8–96.5)</td>
<td>81.8 (53.6–93.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Black</td>
<td>3.1 (0–9.5)</td>
<td>8.1 (1.2–23.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.7 (0–3.2)</td>
<td>0.5 (0–3.7)</td>
<td>0.767</td>
</tr>
</tbody>
</table>

**Table 2: Differences in In-hospital Management (truncated)**

<table>
<thead>
<tr>
<th></th>
<th>HF-ERR ≤1</th>
<th>HF-ERR &gt;1</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB</td>
<td>57.1 (51.1–64.4)</td>
<td>59.6 (50.0–66.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>71.4 (63.7–76.8)</td>
<td>73.0 (66.0–79.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>14.5 (9.5–20.9)</td>
<td>13.4 (8.6–20.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Diuretic</td>
<td>73.2 (52.5–80.7)</td>
<td>69.2 (29.2–77.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anticoagulation for atrial fibrillation</td>
<td>32.7 (27.2–38.6)</td>
<td>31.9 (25.0–36.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Heart failure rehab, % yes</td>
<td>15.2 (0.8–50.0)</td>
<td>3.1 (0–30.2)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Table 3: 1 Year Clinical Outcomes (truncated)**

**In-Hospital and 1-Year Clinical Outcomes Among Heart Failure Patients Across the Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>HF-ERR ≤1</th>
<th>HF-ERR &gt;1</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of mortality or all-cause readmission</td>
<td>62.9 (57.1–66.7)</td>
<td>65.3 (52.9–73.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mortality</td>
<td>31.7 (25.4–34.8)</td>
<td>28.2 (21.4–34.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>All-cause readmission</td>
<td>54.7 (48.3–60.0)</td>
<td>59.1 (48.9–64.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease


Summary
The WOSCOPS (West of Scotland Coronary Prevention Study) was an early primary prevention trial designed to determine the efficacy of statins at preventing future coronary events. The trial enrolled middle aged men with known hyperlipidemia and without known coronary artery disease. Patients assigned to pravastatin had a lower rate of both fatal and non-fatal MIs. Using stored serum samples from the WOSCOPS cohort, the authors of this study sought to assess whether baseline high sensitivity troponin (hs-troponin) concentrations could predict future coronary events, whether these levels could be modified by statins, and whether changes in these concentrations were predictors of future events.

Of over six thousand men originally included in the WOSCOPS cohort, 3,318 participants had plasma samples from enrollment and 1 year available for analysis. The primary outcome was a composite of non-fatal MI and death from coronary artery disease. Trial data was available for 5 years after randomization, and the investigators were able to obtain 15 year data from national health records. All participants were grouped into four quartiles based on their baseline troponin concentration to assess the association with the primary outcome. Both the placebo and treatment arms were then grouped into quintiles based on the change in troponin concentration at 1 year. The relative risks of the primary outcome were assessed using participants in the placebo arm with no change in their troponin concentration as the reference.

As compared to those participants with the lowest baseline troponin concentrations, those with the highest concentrations (> 5.2 ng/L) were at significantly higher risk for MI, death from coronary artery disease, death from cardiovascular disease, and all cause mortality (Figure 1). At 15 years, there was a nearly 7% absolute difference in the primary outcome between those with the highest and lowest baseline troponins. Statin therapy resulted in a 19% reduction in troponin concentration as compared to a 6% reduction in the placebo arm. Decreases in troponin concentrations at 1 year resulted in a significant reduction in the primary endpoint at 5 and 15 years. Participants achieving the greatest reduction in their troponin experienced the largest risk reduction (Figure 2), and those in the statin arm were significantly more likely achieve the largest reduction in troponin concentration.

Commentary
This study contributes to the growing body of evidence supporting the utility of high sensitivity troponins as prognostic biomarkers of cardiovascular risk. Participants with a baseline troponin of greater than 5.2 ng/L were at least three times as likely to experience an event. Statin therapy was remarkably effective at modulating the risk for non-fatal MI and death due to coronary artery
disease. Those in the statin arm with the greatest reductions in troponin concentration had a 5-fold risk reduction in the primary endpoint as compared to those in the placebo arm with the greatest increase in troponin concentration. While the generalizability of these results are limited by the fact that this study enrolled a homogenous population of middle aged European males, the insights gained may have significant therapeutic implications going forward. Statin therapy could be intensified based on these measurements, and adjunct therapy (ie PCSK-9 inhibitors, ezetimibe) could be employed in patients with persistently elevated troponins on maximum dose, high intensity statins.

UTSW Link

Figure 1

Figure 2

REFERENCES

Romosozumab Treatment in Postmenopausal Women with Osteoporosis


Summary
Romosozumab is a monoclonal antibody that inhibits sclerostin, a protein made by osteocytes with anti anabolic effects. This monoclonal antibody also has anabolic effects on bone formation. Prior studies have shown that one year of Romosozumab treatment in postmenopausal woman significantly increased bone mineral density (BMD). The goal of this study was to look at the role of this regimen in postmenopausal women in reducing the risk of fracture. This was a randomized and double-blinded study of 7180 postmenopausal women with a T score -2.5 to -3.5 on Dual-energy X-ray absorptiometry (at the femoral neck or total hip). Patients were assigned either to 1 year of romosozumab (210mg) or placebo monthly for 1 year. After 1 year, each group received 1 year of denosumab (60mg, q6months) given studies showing that follow up treatment with an antiresorptive agent maintains BMD. The primary end point was incidence of new vertebral fractures at 1 and 2 years. Secondary end points included risk of non-vertebral fractures and clinical fractures, which includes non-vertebral fractures and symptomatic vertebral fractures.

Results at 1 year showed an incidence of new vertebral fractures of 0.5% (16 of 3321) in romosozumab group vs. 1.8% (59 of 3322) in placebo group (p<0.001). Non-vertebral fractures in 56 of 3589 in the romosozumab group vs. 75 of 3591 in placebo group (p=0.10). Clinical fractures occurred in 58 of 3589 patients in the romosozumab group vs. 90 of 3591 in the placebo group (p=0.008). At 2 years after treatment with denosumab, there were 21 new vertebral fractures of 3325 in romosozumab group vs. 84 of 3327 in the placebo group (p<0.001).

Commentary
Romosozumab is a new agent that is noted to have the unique dual mechanism of action of targeting both bone resorption and increasing bone formation. The study results suggest that after 1 year of treatment with romosozumab there is a significant reduction in risk of new vertebral fractures. This benefit however was not seen in the risk of non-vertebral fractures. Also, in comparing the adverse events of both groups, the romosozumab group was noted to have slightly more injection site reactions at 1 and 2 years of 5.2% vs. 2.9% (placebo) and 5.2% vs. 3% (placebo), respectively. 1 patient in the romosozumab group also developed osteonecrosis of the jaw at 1 year and an atypical femoral fracture at 1 year. This study may offer a new approach to osteoporosis treatment by both using an agent with a dual mechanism of action and using a sequential two agent method.

UTSW Link
In a carefully written evidence-based review, Forsmark et al. summarize recent advances in acute pancreatitis (AP), clinically defined by the presence of two of the following three criteria: 1) abdominal pain consistent with acute pancreatitis, 2) serum lipase or amylase levels at least 3x ULN, and 3) findings consistent with acute pancreatitis on CT or MRI.

Highlights of the review include:

1. Although gallstones (40%) or alcohol (30%) represent the most frequent causes of AP, 5-10% cases of AP develop as a consequence of ERCP or major surgery such as cardiopulmonary bypass (likely from pancreatic ischemia, and pancreatitis may be severe). Drugs, hypertriglyceridemia, autoimmunity, and genetics are rare causes of AP (<5%).

2. The overall mortality of AP is 2%, but approaches 30% among patients with failure of an organ system (i.e. respiratory, cardiovascular, or renal) or SIRS lasting more than 48 hours despite adequate volume resuscitation. Patients with advanced age (>60 yrs), Charlson comorbidity index ≥2, obesity (BMI ≥30), and long-term heavy alcohol use, or patients with intravascular volume depletion due to third-space losses (manifesting as hemoconcentration [hematocrit >44%] or azotemia [BUN>20 or creatinine>1.8 mg/dL]) are at greatest risk for severe disease, including death, and most likely to benefit from a high-intensity nursing unit.

3. Vigorous crystalloid resuscitation at a rate of 200-500cc/hour or 5-10cc/kg/hour with monitoring of volume status within the first 24 hours provides clear survival benefit. Fluid requirements may be in excess of 4 L per day and, in some cases, can exceed 10 L to maintain adequate volume status. This is not surprising given enormous retroperitoneal third-spacing in AP. Ringer’s lactate seems to be superior to normal saline, presumably due to the anti-inflammatory effect of lactic acid.

4. For mild AP, a low fat diet is recommended in the absence of nausea, vomiting, ileus, and severe pain. In patients with mild AP who do not have organ failure, there is no need for complete resolution of pain or normalization of pancreatic enzyme levels before oral feeding is started. Early initiation of nasoenteric feeding (Dobhoff tube within 24 hours after admission) is not superior to a strategy of attempting an oral diet at 72 hours with tube feeding only if oral feeding is not tolerated over the ensuing 2 to 3 days.

5. There is no role of prophylactic antibiotics in AP unless infection is suspected or confirmed.

6. Nearly 60% of patients with severe necrotizing pancreatitis can be treated noninvasively (or with a step-up approach with a delay in definitive treatment) and will have a low risk of death.

7. Cholecystectomy, preferably during the initial hospitalization in patients with mild AP, prevents recurrent gallstone pancreatitis. A delay of cholecystectomy for more than a few weeks places a patient at a high (up to 30%) risk of relapse.
Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants


SUMMARY
This study pooled 1479 population-based studies of 19.1 million people to estimate blood pressure trends globally from 1975-2015. Analysis was performed by country, region, super-region and by gender, and trends were determined over 4 decades. Blood pressures were noted to decrease in western and Asian Pacific countries and increase in Southeast Asia and sub-Saharan Africa. The authors estimate the prevalence of hypertension increased from 594 million to 1.13 billion, with the majority of the effect being derived from increase in population growth and aging. A hierarchical structure was utilized for estimating national blood pressure data, which allows information to be extrapolated to a greater extent in situations of small sample sizes while allowing for lesser extrapolation when data is plentiful. Data was available for 87% of the countries, covering 97.5% of the world population in the analysis. Overall, no change in mean systolic blood pressure was noted worldwide, however mean systolic and diastolic blood pressure decreased in high-income western and Asia Pacific countries and increased in southeast Asia and sub-Saharan Africa.

COMMENTARY
The NCD Risk Factor Collaboration authors performed a Herculean task assembling 40 years of data on blood pressure measurements representative of 97% of the world’s population. They attempt to form a consistent pool of data by using a unique statistical model that accounts for gaps in the data, however care must be taken in interpretation because portions of the data are extrapolated, particularly in countries where robust patient-level data was not available. Interestingly, their results indicate decreasing blood pressures in high-income Western and Asian countries, while blood pressure increased in poorer countries. The authors do not hypothesize the cause of this finding aside from stating the availability of antihypertensives in the high-income countries along with dietary changes. Additionally, the authors do not state if patients who were taking antihypertensives were included or excluded in their data set, however it does appear patients on antihypertensives were included. Overall, this is a well-done study that provides important information on blood pressure trends globally.

UTSW Link
Effect of Cognitively Stimulating Activities on Symptom Management of Delirium Superimposed on Dementia: A Randomized Controlled Trial


Summary
In this single blind, randomized controlled trial, the authors seek to determine whether individualized cognitively stimulating activities reduce the duration and severity of delirium and improve function in patients with delirium superimposed on dementia (DSD) in the post-acute care setting. Participants were 65 and older, community dwelling before hospitalization, and had mild to moderate dementia. 283 patients were randomly assigned to cognitive simulation or usual care.

The intervention engaged patients in simple activities to provide cognitive stimulation and promote attention, memory, orientation, and executive function. Activities were selected from a database that was previously tested in older adults with dementia. The activities were individually selected for each patient based on their interests in order to optimize engagement and attention. The intervention was conducted in individualized sessions by research assistants for up to 30 minutes per day, 5 days per week, for 30 days or until discharge.

There was no significant difference between the intervention and usual care groups in mean percentage of delirium-free days (64.8% vs 68.7%), time to first remission of delirium (6.88 vs 7.39 days), percentage of patients with delirium symptoms at discharge or completion of intervention (62.3% vs 65.2%), or severity of delirium on the Delirium Rating Scale. There was a statistically significant improvement in executive function (assessed using the CLOX test with a clock drawing task) in the intervention group compared to the control group, but there was no difference between the groups in other cognitive domains or physical function. The average length of stay at the post-acute care facility was 36.1 days for the intervention group and 53.1 days for the usual care group (p = 0.01). 32.6% of intervention patients were discharged back to the community compared to 27.5% of usual care patients, but this difference was not statistically significant (p = 0.54).

Commentary
At least 20% of hospitalized adults over age 65 will develop delirium, and underlying dementia is the strongest risk factor. Delirium may take weeks to months, and occasionally even years, to resolve. Additionally, delirium may alter the trajectory of an underlying dementia, with a more rapid decline in cognitive and functional status. Treatment of delirium focuses on symptom management. Non-pharmacological interventions have been proven effective for prevention of
delirium, but there is not strong evidence for use in treatment of delirium, which this study aims to address.

The study finds only a small improvement in executive function associated with the cognitive stimulation intervention. It is unclear whether this improvement was clinically significant or not, but executive function is important for independence. It is possible that with a longer intervention or longer follow up, greater improvements might have been seen. The authors postulate that the outcome measures used to evaluate cognitive function may not have been sensitive enough to detect smaller improvements.

The intervention was also associated with a shorter length of stay in the post-acute care facility. This difference persisted between the intervention and usual care group when controlling for the effect of facility. There was no difference in ultimate disposition (home vs other facility) between the two groups, but it seems that the cognitive stimulation intervention may have shortened time to discharge, which may be meaningful for healthcare cost reduction.

**REFERENCES**

**Hematology & Oncology**

**Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and puerperium**


**Summary**

The objective of this study was to analyze the risk factors associated with venous thromboembolism (VTE) in women during pregnancy and to improve thromboprophylaxis management. This was a retrospective, case-control study that reviewed 243 patients with a history of first VTE during pregnancy or peripartum along with 243 control patients. The control patients had >1 prior pregnancy with no history of VTE. No subjects in either group showed evidence of autoimmune disease or malignancy. Women with antiphospholipid syndrome were excluded.

All patients underwent whole blood sampling. The testing occurred > 3 months post-partum or >6 months after VTE to exclude any thrombosis and/or inflammation related effects of the test results. Testing included antithrombin activity, plasma proteins C and S levels, lupus anticoagulant, cardiolipin, B2-glycoprotein, presence or absence of factor V Leiden (FVL) and prothrombin G20210A mutation.

Slightly more (54.3%) of the VTEs occurred during pregnancy versus postpartum with a majority occurring in the third trimester (75%). Not surprising, FVL homozygous patients had a 17.2 times higher risk of VTE (95% CI, 6.3-47) than those unaffected. Thirteen patients in the VTE group had a compound heterozygosity for both FVL and prothrombin G20210A. No women in the control group were found to have this combined defect. This proved to be a significant risk with an OR 49 (95% CI, 26-84). Severe deficiency in antithrombin (levels <60%), protein C (levels <50%), and protein S (levels <40%) were associated with high OR, 49 (CI 95%, 11.5 – 204), OR 5.5 (1.8 – 17.3), and OR 4.1 (0.84-19.9) respectively. A positive family history of thrombosis in first-degree relatives increased the risk of VTE by 3.3% (95% CI 2.2-5).

**Commentary**

Pregnancy associated VTE is an important cause of maternal morbidity and mortality. Pregnant patients have a 5 times higher risk than the normal population, however the absolute risk remains low. The risk of VTE is multifactorial with both acquired and hereditary risk factors playing a role. This study set out to quantify the influence of heritable thrombophilias on the risk of thrombosis. The importance of understanding the interaction and magnitude of these risk factors is to establish guidelines for thromboprophylaxis. Current recommendations for prophylactic anticoagulation include patients with homozygous FVL and positive family history of VTE. This study demonstrated that a compound defect of heterozygous FVL and prothrombin G20210A is
associated with a particularly high risk of pregnancy associated VTE. This data provides evidence to support routine thromboprophylaxis in these patients as well. But the question still remains, who should be screened for these genetic mutations. Patients with other thrombophilia risk factors including age >35, obesity, and smokers would most likely benefit from screening. Further studies are needed to determine the safety and efficacy in this group of patients before official recommendations can be made.

UTSW Link
Nonselective β-blockers do not affect mortality in cirrhosis patients with ascites: Post Hoc analysis of three randomized controlled trials with 1198 patients


SUMMARY

Non-selective beta blockers (NSBB) have been used for decades in primary and secondary prevention of variceal bleeding in patients with cirrhosis. Surprisingly, an observational study published in 2010 showed that NSBB increase mortality in cirrhotics with refractory ascites or spontaneous bacterial peritonitis (SBP), raising serious concerns about the safety of NSBB patients with end-stage cirrhosis.¹ This, along with other studies published at that time, led to an expert opinion (also known as the “NSBB window hypothesis”) that NSBB should be discontinued in patients with refractory ascites or SBP. This recommendation was perceived as controversial as these findings were not replicated in subsequent observational studies.

The uncertainty raised by the aforementioned studies has been clarified in a recently published paper by Bossen et al., who performed a multicenter RCT with a total of 1198 patients to investigate whether NSBB treatment is associated with increased mortality in cirrhotic patients as well as in subgroups with decompensated disease. The 1-year mortality was 23% in NSBB users and 25% in nonusers (no statistically significant difference). In addition, in the 588 patients with refractory ascites, mortality was not increased by NSBB treatment (adjusted hazard ratio, 1.02; 95% confidence interval, 0.74-1.40). The use of NSBB was also not associated with increased mortality in patients with a history of SBP.

COMMENTARY

The “NSBB window hypothesis” states that NSBB are of no benefit in early stages of cirrhosis when there are no esophageal varices and the effect of NSBB on portal pressure is very small, and that the “NSBB window opens” in patients with medium-large varices or who have bled, providing survival benefit.² However, determining the timing of “NSBB window closure” has been difficult. Theoretically, NSBB could reduce survival in patients with decompensated cirrhosis and ascites due to negative impact on the cardiac compensatory reserve and interference with organ perfusion during stress or intercurrent illness. However, no high-quality data confirms the applicability of this concept to the clinical scenario. Based on the “NSBB window hypothesis”, some authors have recently recommended that NSBB may need to be stopped if the patient develops ascites that becomes refractory to treatment, and the UK guidelines updated last year recommend that NSBBs should be discontinued at the time of SBP, renal impairment, or hypotension.³ Some of these new recommendations have now been contradicted in this well-designed RCT by Bossen L et al., who demonstrate that NSBB do not increase all-cause or
cirrhosis-related mortality, and that they are safe in patients with refractory ascites and in patients with a history of SBP. With that in mind, what then are the indications for stopping NSBBs? It was agreed upon at the Baveno VI consensus conference that NSBBs in cirrhotics should be held in life-threatening situations (GI bleeding, hepatorenal syndrome, sepsis) or, in patients who have refractory ascites, NSBBs should be reduced or discontinued when systolic blood pressure is <90 mm Hg, when serum sodium concentration is <130 mEq/L, or in cases of acute kidney injury.  

**UTSW Link**

**REFERENCES**

Unnecessary Hospitalization and Related Harm for Patients With Low-Risk Syncope  


SUMMARY

The San Francisco Syncope Rule (SFSR) is a decision aid tool designed to identify patients presenting to the emergency room with syncope who are at very low risk for short term adverse outcomes.1, 2 The SFSR uses five different criteria: history of congestive heart failure, hematocrit less than 30%, abnormal EKG (new changes or non-sinus rhythm), shortness of breath, or a systolic blood pressure of 90 mmHg or less at triage. Patients not meeting any of these criteria are deemed “low-risk” and are considered appropriate for discharge from the emergency department.

The authors identified 507 admissions over a two-year period with a primary diagnosis of syncope. Participants were excluded if there was an alternative reason for admission (including intoxication) or were directly admitted or transferred. Of the remaining admissions, 72 (34%) were for low risk syncope (SFSR score of 0). These patients underwent extensive inpatient testing (Table 1). Notably, 88% percent of these patients had a head CT performed, 64% had a transthoracic echocardiogram, and 93% percent were placed on telemetry monitoring. Inpatient testing led to 23% of patients having “incidental findings of unclear significance” (Table 2), including newly identified pulmonary nodules, mild aortic stenosis, and intracranial aneurysms. Only 7% of patients had “potentially beneficial incidental findings” that lead to therapeutic interventions. Most concerning was an adverse event rate of 13% with four of eleven events defined as serious.

COMMENTARY

While the etiology of syncope is often unknown or simply attributed to a vasovagal episode3, the potential for missing cardiovascular and/or neurologic causes often drives clinicians to order extensive (and expensive) testing. The combination of history, physical, and EKG alone can identify the etiology of syncope in approximately 50% of patients.4, 5 Well-validated decision tools like the SFSR used in combination with our history and physical should ideally help avoid unnecessary, costly hospitalizations and testing. While this was a single center, retrospective study without any long term follow up, its findings are still noteworthy. 1/3rd of patients deemed to be at very low risk for serious outcomes were still hospitalized, with less than 10% of these hospitalizations resulting in findings that had clear clinical relevance. The rate of incidental findings in this study is especially alarming, and half of the participants with incidental findings required further outpatient evaluation. Knowing when not to perform an intervention is often just as important as knowing when to do something, and in the case of low risk syncope, no is probably the right answer.

UTSW Link
References


Infectious Diseases

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women


SUMMARY

Antiretrovirals (ARVs) have proven to be effective in preventing transmission and acquisition of HIV. In this multicountry phase 3 randomized double-blind placebo-control trial, a monthly vaginal ring containing dapivirine was randomized among HIV negative women to test its effectiveness in preventing HIV infection when compared to placebo. Over 2600 women ages 18 to 45 were enrolled with about 1300 on each arm of the study. The main study endpoint was acquisition of HIV during a median follow-up period of 1.6 years. During the study period, a total of 168 women became HIV positive with 71 in the dapivirine group and 97 in the placebo group. This equated to an incidence of 3.3 in the dapivirine group compared to 4.5 per 100 person years in the placebo group, which was a 27% lower incidence (95% CI: 1 to 46; P=0.046). Participant adherence to monthly use of the ring was assessed by measuring plasma dapivirine levels. Two of the 15 study sites were found to have suboptimal adherence. When these two sites were excluded from the analysis, the incidence of HIV acquisition in the dapivirine group decreased and was 37% lower than the placebo group (95% CI 12 to 56; P=0.007). Overall, this study demonstrated that dapivirine containing vaginally ring is efficacious in protecting women from acquiring HIV especially in the setting of close adherence to the product.

COMMENTARY

Modes of effective HIV prevention have long been sought after and at times been elusive in the case of a vaccine. The use of ARVs has been promising because now there is strong evidence that they prevent HIV transmission. However, prevention of HIV acquisition with ARVs has been more challenging due to poor adherence to daily use of oral therapy such as Tenofovir-based prophylaxis or vaginal gels. These previous modalities have thus proven to be ineffective. In this study, the vaginal ring containing dapivirine was effective in reducing HIV infection likely partially due to the ease of monthly use. Adherence to the ring was still an issue faced in the study. This brings to question whether drug delivery could be even more simplified such as a monthly injection or combined with an oral contraceptive, which many women would be more willing to take daily.

UTSW Link
Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism Two Randomized Clinical Trials


Summary
Secondary hyperthyroidism is a common complication of chronic kidney disease that leads to bone and cardiovascular disease, and is associated with an increased all-cause and cardiovascular mortality. Prior studies showed that a PTH concentration greater than 600 was independently associated with a 15% increased risk of mortality compared to PTH levels between 150 and 600. Etelcalcetide is a synthetic peptide which binds the calcium-sensing receptor at a different location than that of cinacalcet that has been shown in laboratory animals to significantly reduce PTH and serum calcium. This JAMA article publishes the results of two randomized, placebo-controlled trials which were done to evaluate the safety and efficacy of etelcalcetide in lowering serum PTH in hemodialysis patients.

The studies lasted for 26 weeks and included 1023 patients on hemodialysis with moderate to severe hyperparathyroidism (PTH >400) from more than 100 sites in the United States, Canada, Europe, Israel, Russia and Australia. At baseline, patients had a mean PTH in the 800s and were receiving conventional treatment for secondary hyperparathyroidism, including phosphate binders and calcitriol or active vitamin D analogs. The dose of etelcalcetide was titratable up to 15 mg in order to achieve a PTH of 300 pg/mL or lower. Patients receiving etelcalcetide were much more likely to achieve a 30% reduction of their baseline PTH (74% vs 8.3% in trial A; 75.3% vs 9.6% in trial B) and were much more likely to achieve a PTH level of 300 pg/mL or lower (49.6% vs 5.1% in trial A; 53.3% vs 4.6% in trial B). The average PTH concentrations at baseline and 5-7 months later were 849 and 384 in the etelcalcetide group versus 820 and 897 in the placebo group. However, there were no differences in rates of death, myocardial infarction, stroke, or seizure between the study and placebo groups.

The most common adverse event in the etelcalcetide group was hypocalcemia, and the etelcalcetide group had a significant increase in their use of dialysate calcium and oral calcium and vitamin D. Other adverse events that were more frequent in the etelcalcetide group included nausea, vomiting, and diarrhea, as well as several symptoms which may be attributable to hypocalcemia, including muscle spasms, headache, and paresthesia.

Commentary
The strengths of the study include the diversity of its participants as well as its high retention rates. The high retention rate is particularly notable, as prior studies of cinacalcet, one of the first
calcimemtics, had two-thirds of patients discontinue the study drug. However, clinical applications of this study are limited, given the lack of definite clinical benefits, such as decreased risk of fracture, cardiovascular events, or mortality, which is similar to the findings of prior cinacalcet studies. Additional longer-term studies are needed to further assess the clinical benefit of calcimimetics and address further safety concerns, including the risk of significant increases in the calcium balance of patients treated with etelcalcetide.

UTSW Link
Table A: Mean Percentage Change From Baseline by StudyWeek in Parathyroid Hormone, Corrected Calcium, and Phosphate Concentrations by Randomized Group in Each Trial
Quality of End-of-Life Care Provided to Patients with Different Serious Illnesses


Summary

Inpatient end of life care is an important topic as more patients are spending their final days inside of a hospital or nursing home. This article is a retrospective analysis of veteran patients with various medical illnesses who died between 2009 and 2012. All 146 of the hospitals within the Veteran Affairs (VA) health systems were utilized and the clinical diagnoses evaluated were cancer, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), dementia, end-stage renal disease (ERSD) and frailty. Data was obtained from VA’s medical records and a bereaved family member survey conducted by the Performance Reporting and Outcomes Measurement to Improve the Standard of Care at the End-of-life (PROMISE) Center. Exclusion criteria included patients who died secondary to suicide or less than 24 hours after being admitted to a VA facility. There were 57,753 deaths during the study period and 34,005 had family members who completed the study survey. Outcomes associated with high quality of care included palliative care consultation in the last 90 days of life, do-not-resuscitate order at the time of death, and death in a hospice or palliative care unit. Death in the intensive care unit was considered a negative quality indicator as it was associated with a lower quality rating from families. The patient family survey was based on family’s global rating of quality on a 5-point Likert scale and questions regarding perception of provider communication, emotional support and medical treatment provided. Study results showed that roughly half of patients with COPD, CHF or frailty received palliative care consultations compared to 74% of patients with cancer and 61% of those with dementia. Moreover, about 1/3 patients with COPD, CHF, ESRD or frailty died in the ICU which was more than double rate for patients with cancer or dementia (13.4% and 8.9%, respectively). More families rated the quality of end-of-life care as excellent for decedents with cancer and dementia than families of patients with COPD, CHF, ESRD, or frailty.

Commentary

Based on this study the quality of end-of-life care for patients with end-organ failure was generally lower than for patients who had cancer or dementia. This disparity was seen in the analysis of established measures regarding the quality of end-of-life care and family survey results. However, this study had a few limitations, the entire cohort was done with the VA population which may not be generalizable to patients in non-VA health care systems. Furthermore, only 64% of patients who died had family members complete the bereaved survey which could correspond to a nonresponse bias of family quality study results. Future strategies to reduce the disparity in the quality of end-of-life care include increasing access to palliative care and increasing goals of care discussions that address code status and preferred setting of death. Overall, this study shows that
health professions need to do a better job in assisting and planning end-of-life care in patients with terminal illnesses other than cancer and dementia.

**UTSW Link**

**Table:** Adjusted Proportions for Measures of Care at the End of Life and Family Perceptions of Quality Outcomes by Diagnosis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. (%)</th>
<th>Cancer</th>
<th>Dementia</th>
<th>ESRD</th>
<th>Cardiopulmonary Failure</th>
<th>Futility</th>
<th>Other</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All veteran decedents (n = 57 728)c</td>
<td></td>
<td>23 523 (40.8)</td>
<td>3675 (6.4)</td>
<td>2265 (3.9)</td>
<td>13 854 (24.0)</td>
<td>9931 (17.2)</td>
<td>4480 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Measures of care at the end of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative care consultation</td>
<td></td>
<td>73.5</td>
<td>61.4</td>
<td>50.4</td>
<td>46.7</td>
<td>43.7</td>
<td>41.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Do-not-resuscitate order</td>
<td></td>
<td>95.3</td>
<td>93.5</td>
<td>87.0</td>
<td>86.3</td>
<td>88.6</td>
<td>83.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Died in inpatient hospice</td>
<td></td>
<td>42.9</td>
<td>32.3</td>
<td>24.3</td>
<td>22.9</td>
<td>20.3</td>
<td>20.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Died in the intensive care unit</td>
<td></td>
<td>13.4</td>
<td>8.9</td>
<td>32.3</td>
<td>34.1</td>
<td>35.2</td>
<td>37.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Bereaved Family Survey participants (n = 34 005)d,e</td>
<td></td>
<td>40.3</td>
<td>6.6</td>
<td>3.7</td>
<td>24.4</td>
<td>17.4</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Overall rating of patient's care was excellent</td>
<td></td>
<td>59.2</td>
<td>59.3</td>
<td>54.8</td>
<td>54.8</td>
<td>53.7</td>
<td>55.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Health care professionals always listened to concerns</td>
<td></td>
<td>73.8</td>
<td>75.7</td>
<td>68.6</td>
<td>71.5</td>
<td>70.5</td>
<td>73.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Health care professionals always provided the medical treatment that patient and family wanted</td>
<td></td>
<td>79.1</td>
<td>80.4</td>
<td>73.4</td>
<td>76.8</td>
<td>76.5</td>
<td>77.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Health care professionals always kept family informed about patient's condition and treatment</td>
<td></td>
<td>68.2</td>
<td>71.1</td>
<td>63.8</td>
<td>65.9</td>
<td>66.6</td>
<td>67.5</td>
<td>.001</td>
</tr>
<tr>
<td>Health care professionals always gave enough emotional support prior to the patient's death</td>
<td></td>
<td>64.6</td>
<td>67.5</td>
<td>61.5</td>
<td>62.1</td>
<td>62.0</td>
<td>63.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Patient had frequent uncontrolled pain</td>
<td></td>
<td>55.0</td>
<td>49.4</td>
<td>54.3</td>
<td>55.9</td>
<td>53.3</td>
<td>55.3</td>
<td>.003</td>
</tr>
</tbody>
</table>
Addressing Unmet Basic Resource Needs as a part of Chronic Cardiometabolic Disease Management

Dr. Sarah Kiani reviewing Berkowitz et al. JAMA Intern Med, Published online December 12, 2016.

SUMMARY
The aim of this study was to determine if access to basic resource needs impacts management of chronic cardio-metabolic diseases. The effect of the Health LEADs program on blood pressure, LDL-C levels and hemoglobin A1C values was assessed by means of a retrospective cohort that included three academic primary care centers in Boston. As a part of the Health LEADs program, patients' self-identified need for unmet basic resources namely food, medication, transportation, utilities, employment, eldercare services and housing. Those who screened positive were offered enrollment in the program and those who chose to enroll were assigned an advocate who helped them attain access to community resources the patients qualified for. Statistically significant decreases in systolic & diastolic blood pressure and LDL-C levels were seen after enrollment amongst patients who identified the presence of unmet basic resources and enrolled in the program compared to those who did not enroll. No statistically significant difference was seen in hemoglobin A1C levels between the groups after enrollment.

COMMENTARY
Within the last decade, the recognition of social determinants of health has rekindled the need for healthcare reforms to improve access to basic needs. Community health workers (CHW), Social Workers (SW) and Case Managers (CM) have been introduced to improve patient access to resources available for the management of acute and chronic illnesses. Accountable Health Communities is a Centers of Medicare and Medicaid project that aims to provide capital for development of infrastructure for medical practices to improve identification and referral of patients in need for such support. Traditionally, this is accomplished through CHW/SW/CM. The Health Leads program, in contrast, utilized the services of student volunteers for identification and referral of patients who screened positive via self-screening. By means of a retrospective review, the authors tried to investigate if screening and addressing unmet basic needs improved cardiometabolic disease management.

Retrospective Cohort Trials are not as robust as Randomized Control Trials in dealing with confounders. Patient's self-identification of unmet needs and enrollment in the program based on personal preference may reflect different health consciousness and behaviors. It is also not certain, if after the referral, to what degree the resources were utilized, if at all. Although the authors mention in the discussion that this process may be less costly due to the services of volunteers instead of employed professionals, a comparison of the relative efficacy and costs of both models needs to be evaluated.
The creation of the first public health department in London in the 19th century can be traced back to identification of disease epidemics in low income households in the city. In the past decade, there has been a resurgence of interest in the effects of quality of life on population health. This study shows that screening and addressing unmet basic resource needs may improve cardiovascular disease outcomes; the modest change seen in the Health Leads group in comparison to those that refused enrollment is associated with approximately 4-5% reduction in relative risk of coronary heart disease events.\textsuperscript{3,4}

With the healthcare sector’s increasing role in the identification and referral of patients to ensure provision of basic resource needs, which was previously the government’s function, what remains to be answered is whether this division of responsibility will be more successful for the improvement of health of the population. The answer will greatly determine the distribution of resources.

**UTSW Link**

**References**

ACOs Serving High Proportions of Racial and Ethnic Minorities Lag In Quality Performance


Summary

Accountable Care Organizations (ACOs) are groups of physicians that are responsible for the complete care of a defined population of patients. This model of healthcare delivery began in 2011. The goal is to improve both quality and cost effectiveness of care. ACOs in the Medicare Shared Savings Program (MSSP) have the opportunity to share in cost savings that they achieve relative to The Centers for Medicare and Medicaid Services (CMS) established-benchmarks, incentivizing quality outcomes. CMS defines a variety of quality outcomes that factor into an overall quality composite score for an ACO that determines the share of savings the ACO will receive.

The authors of this study conducted cross-sectional and longitudinal analyses of quality performance of ACOs in the MSSP during the first two years of their participation from 2012-2014, with particular attention to the racial composition of the patients in the ACOs. Data was obtained from the MSSP and from the National Survey of Accountable Care Organizations conducted by the Dartmouth Institute for Health Policy and Clinical Practice. There were 306 Medicare ACOs with complete data available for their first year of participation and 191 with complete data for their second year of participation.

17.8% of patients in the ACOs were minorities- 10.2% black, 2.6% Hispanic, 0.2% Native American, 2.4% Asian, and 2.4% another race. A small number of ACOs took care of most of the minority patients. The top 5% of ACOs in terms of proportion of minority patients had populations consisting of greater than 50% minorities. Among the top quartile of ACOs in proportion of minority patients, each cared for populations made up of greater than 25% minorities. Compared to the other 75% of ACOs, these patients were more likely to be younger than 65, dually eligible for Medicare and Medicaid, disabled, female, and to have end stage renal disease. There were no significant differences between the ACOs in the top quartile of proportion of minority patients and the others in number of clinicians or proportion of primary care providers (Exhibit 1). The ACOs in the top quartile of proportion of minority patients were less likely to offer specialty care (57% vs 75%), outpatient rehabilitation (29% vs 50%), pediatrics (40% vs 59%), and palliative and hospice care (30% vs 53%).

Using multivariate regression analysis, the proportion of minority patients was associated with worse performance on 29 of 36 quality measures. This number decreased to 25 of 36 quality measures when adjusted for patient and ACO characteristics (Exhibit 2). These disparities
persisted from year one to year two, indicating that ACOs with higher proportions of minority patients did not improve quality outcomes at a faster rate than others.

**Commentary**

It is well known that there are disparities in access to healthcare as well as health outcomes between whites and minority patients in the United States. Based on this study, it seems that these disparities persist in ACOs. It is important to note that this analysis did not control for many patient-level characteristics, specifically socioeconomic factors (e.g. education, income, health literacy, neighborhood factors), that may contribute to or explain the association between the racial composition of the ACO and quality outcomes. Nonetheless, the study raises the concerns that 1) racial minorities receive poorer quality of care than whites and 2) under the current incentive structure, ACOs may be deterred from caring for panels with larger proportions of minority patients because they receive a smaller share of the cost savings based on lower quality outcome scores. Future studies should address why these racial disparities persist and what underlying factors can be addressed. Policy makers should consider accounting for socioeconomic factors of the patient population when determining quality outcomes scores and reimbursements, so as not to deter providers from caring for underserved populations. Further, we should consider what additional support and resources ACOs that care for underserved populations may require to bridge the gap in quality outcomes.

[UTSW Link]
**EXHIBIT 2**

Associations between the proportion of minority patients and accountable care organization (ACO) performance on quality measures, unadjusted and adjusted for patient population characteristics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
<th>Regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Quality composite*</td>
<td>62.7</td>
<td>(6.2)</td>
<td>-17.7****</td>
</tr>
<tr>
<td><strong>PATIENT EXPERIENCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting timely care</td>
<td>81.0</td>
<td>(3.2)</td>
<td>-8.4****</td>
</tr>
<tr>
<td>How well your doctors communicate</td>
<td>92.7</td>
<td>(1.6)</td>
<td>-4.3****</td>
</tr>
<tr>
<td>Patient's rating of doctor</td>
<td>91.9</td>
<td>(1.6)</td>
<td>-3.2****</td>
</tr>
<tr>
<td>Access to specialists</td>
<td>84.9</td>
<td>(2.2)</td>
<td>-3.2****</td>
</tr>
<tr>
<td>Health promotion and education</td>
<td>58.0</td>
<td>(3.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>Shared decision making</td>
<td>74.5</td>
<td>(2.3)</td>
<td>-4.6****</td>
</tr>
<tr>
<td>Health or functional status</td>
<td>70.9</td>
<td>(2.2)</td>
<td>-4.7****</td>
</tr>
<tr>
<td><strong>CARE COORDINATION AND PATIENT SAFETY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause unplanned readmissions</td>
<td>15.0</td>
<td>(0.8)</td>
<td>2.0****</td>
</tr>
<tr>
<td>Admissions for COPD or asthma</td>
<td>1.1</td>
<td>(0.4)</td>
<td>0.6****</td>
</tr>
<tr>
<td>Admissions for CHP</td>
<td>1.2</td>
<td>(0.2)</td>
<td>0.3****</td>
</tr>
<tr>
<td>PCPs qualifying for EHR incentive pay</td>
<td>69.7</td>
<td>(20.0)</td>
<td>-46.0****</td>
</tr>
<tr>
<td>Medication reconciliation after discharge</td>
<td>78.1</td>
<td>(24.7)</td>
<td>2.4</td>
</tr>
<tr>
<td>Screening for fall risk</td>
<td>38.6</td>
<td>(22.7)</td>
<td>-8.9</td>
</tr>
<tr>
<td><strong>PREVENTIVE HEALTH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza immunization</td>
<td>55.3</td>
<td>(14.4)</td>
<td>-18.1****</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>52.7</td>
<td>(19.0)</td>
<td>-41.4****</td>
</tr>
<tr>
<td>Adult weight screening and follow-up</td>
<td>62.1</td>
<td>(15.8)</td>
<td>1.4</td>
</tr>
<tr>
<td>Tobacco use assessment and cessation</td>
<td>84.9</td>
<td>(13.5)</td>
<td>-12.6****</td>
</tr>
<tr>
<td>Depression screening</td>
<td>30.0</td>
<td>(22.3)</td>
<td>1.8</td>
</tr>
<tr>
<td>Colorectal cancer screening</td>
<td>56.9</td>
<td>(14.4)</td>
<td>-27.7****</td>
</tr>
<tr>
<td>Mammography screening</td>
<td>60.5</td>
<td>(13.6)</td>
<td>-27.7****</td>
</tr>
<tr>
<td>High blood pressure screening</td>
<td>69.3</td>
<td>(23.3)</td>
<td>16.9</td>
</tr>
<tr>
<td><strong>POPULATIONS AT RISK BECAUSE OF:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (composite)*</td>
<td>22.1</td>
<td>(11.1)</td>
<td>-21.2****</td>
</tr>
<tr>
<td>Hypertension (controlling high blood pressure)</td>
<td>67.6</td>
<td>(8.2)</td>
<td>-12.2****</td>
</tr>
<tr>
<td>IVD (complete lipid panel and LDL control)</td>
<td>55.1</td>
<td>(12.0)</td>
<td>-22.3****</td>
</tr>
<tr>
<td>IVD (aspirin use)</td>
<td>78.0</td>
<td>(15.2)</td>
<td>-31.2****</td>
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<tr>
<td>Heart failure (beta-blocker therapy for LVSD)</td>
<td>83.0</td>
<td>(15.5)</td>
<td>2.5</td>
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<td>Coronary artery disease (composite)*</td>
<td>64.2</td>
<td>(15.3)</td>
<td>-13.8**</td>
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Quality Improvement

Alternative Strategies to Inpatient Hospitalization for Acute Medical Conditions: A Systematic Review


SUMMARY

Citing the more than 30 percent share of healthcare spending accounted for by hospital-based care, Conley et al assess in this systematic review alternative models in the management of acute medical conditions. The interventions fit squarely into one of four categories: 1) outpatient management for which triage occurs in the ED or clinic setting followed by close follow-up; 2) quick diagnostic units (QDU) or organized clinics intended for rapid diagnosis of serious illnesses; 3) hospital-at-home (HaH), which require triage in the ED or clinic followed by at-home care; and 4) observation units built for protocol-driven management for up to 48 hours. Studies on outpatient management constitute the most robust pool of data amongst these and focus on management of DVT/PE, chemotherapy-induced febrile neutropenia and CAP. HaH interventions focused on low-risk cases of COPD and heart failure exacerbation as well as CAP, urosepsis and cellulitis, observation units on chest pain, atrial fibrillation, asthma, COPD and pyelonephritis, and QDUs on a variety of other conditions including malignant neoplasm and unexplained anemia.

All four interventions were associated with no significant difference in mortality and with substantial cost savings—ranging from about $500 per patient for observation units to $2000 per patient for HaH and $3000 per patient for QDUs—as compared to inpatient management. Readmission rates were unchanged for outpatient management, and not significantly changed for HaH and observation units, though the one study of QDUs did demonstrate an increase in readmissions. Patient and caregiver satisfaction was high across the board for these interventions as well, though not examined in studies of observation units.

COMMENTARY

The potential for cost-savings and an improved patient experience is an encouraging finding in the current climate of healthcare reform. Interventions for reducing or eliminating inpatient stays may well be instrumental in reducing costs but will require an emphasis on effective triage and clear accountability for cases where follow up is indicated. Results presented here are, however, primarily descriptive and hypothesis-generating given the poor quality of evidence, likelihood for confounding bias and heterogeneity of the interventions themselves. Successful implementation of outpatient strategies will require further research to describe low risk candidates, test in a randomized controlled setting these interventions against traditional management, and describe qualitatively the specific aspects of HaH and observation units that improve satisfaction so that these may be replicated and implemented efficiently.

UTSW Link
Cardiovascular Safety of Celecoxib, Naproxen or Ibuprofen for Arthritis


Summary

Celecoxib is an NSAID that inhibits cyclo-oxygenase 2 (COX-2), in contrast to non-selective members of its class, which act on both COX-1 and COX-2. The PRECISION trial is a randomized, multicenter, double blind, non-inferiority trial conducted to assess cardiovascular (CV), gastrointestinal (GI), renal, and other outcomes of celecoxib as compared with two non-selective NSAIDs, naproxen and ibuprofen. Included subjects (N=24,081) had osteoarthritis or rheumatoid arthritis requiring daily treatment with NSAIDs, as well as established CV disease or an increased risk of the development of CV disease. Patients were randomized in a 1:1:1 ratio to receive celecoxib 100mg BID (increased up to 200mg BID), naproxen 75mg BID (increased up to 500mg BID), or ibuprofen 600mg TID (increased up to 800mg TID). All patients were prescribed esomeprazole for gastric protection. The primary outcome was (time to event for) a composite outcome of CV death, nonfatal MI, or nonfatal stroke. Celecoxib was found to be non-inferior in primary outcome rates as compared to both naproxen and ibuprofen (hazard ratios from intention-to-treat analyses 0.93 [95% CI 0.76-1.13, p<0.001] and 0.85 [95% CI 0.70-1.04, p<0.001], respectively). Celecoxib was also non-inferior in secondary outcomes (including overall fatal events, nonfatal CV events, serious GI events, and renal events), while demonstrating lower rates of serious GI events as compared to naproxen and lower rates of GI and renal events as compared to ibuprofen. Incidentally, study subjects reported overall better control of pain with naproxen relative to celecoxib or ibuprofen.

Commentary

The COX enzyme exists in 2 isoforms – COX-1 is a ubiquitous isozyme that produces prostaglandins including those that regulate GI mucosal integrity, whereas COX-2 is predominantly cytokine-induced and produces prostaglandins that mediate pain and inflammation. The description of these two isoforms in the late 1990s led to the development of specific COX-2 inhibitors in the hope that these would be better tolerated than their non-selective counterparts. However, the first trials of COX-2 inhibitor rofecoxib showed a worrisome association with increased rates of myocardial infarction and stroke as compared to placebo.1 Another study of COX-2 inhibitors valdecoxib and parecoxib demonstrated increased CV events as compared to placebo when used for postoperative pain after cardiac surgery.2 Similar concerns over celecoxib arose with results from NCI's Adenoma Prevention with Celecoxib (APC) trial, in which a 2- to 3-fold increased risk of serious CV events was seen for celecoxib as compared to placebo.3 In light of these findings, rofecoxib was voluntarily withdrawn by its manufacturer, the APC trial was halted prematurely based on interim data, and the FDA issued a statement.
cautioning physicians to evaluate alternative therapy while a mandated CV safety trial for celecoxib (the PRECISION trial) was underway.

Since the APC trial, additional data have demonstrated non-inferiority of celecoxib in terms of CV risk as compared to placebo \(^4\) and non-selective NSAIDs \(^5,6\). The PRECISION trial is the most recent study with findings supporting relative safety of celecoxib as compared to ibuprofen and naproxen. Of note, the maximum daily dose of celecoxib (200 to 400mg) was intentionally selected, as higher doses (800 mg daily) had been associated with higher risk for CV events in the APC trial. Limitations of the PRECISION trial included lower rates of [medication] adherence and retention than those reported in previous studies. Still, adherence and retention were equal in all study arms, and results from intention-to-treat and per-protocol analyses were comparable.

In conclusion, findings from the PRECISION trial may help dispel physician concerns regarding the safety of celecoxib over non-selective NSAIDs. Indeed, its preferential use in patients with a history of gastritis or peptic ulcer disease may be prudent given its improved GI safety profile. Nevertheless, increased risk of serious adverse CV and GI events remains a class effect of all NSAIDs and continued judicious use is warranted in at-risk populations.\(^7\)

**UTSW Link**

**REFERENCES**

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