The Top Five Papers of 2020 for General Internists

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Abstract
The Canadian Society of Internal Medicine (CSIM) held an annual session to present the “Top 5 papers” influencing the practice of general internists. We reviewed major journal publications from January 2020 to November 2020 to come up with approximately 10 articles we considered practice changing trials for general internists. Out of those papers, we decided to present the five we considered were most relevant by addressing frequent pathologies seen in practice, were methodologically well conducted, and had the potential to sustainably modify practice guidelines. The references to the papers that were not retained are presented in the bibliography section for the reader’s interest. This article aims to present those top five papers of 2020, and to review their strengths and limitations. These articles were also discussed at the CSIM Virtual Educational Activity on October 15, 2020 and in the BaladoCritique podcast.

Résumé
La Société canadienne de médecine interne (SCMI) a tenu une séance annuelle pour présenter les « cinq meilleurs articles » qui influencent la pratique des internistes généralistes. Nous avons examiné les publications des principales revues publiées entre janvier 2020 et novembre 2020 pour en arriver à proposer environ dix articles que nous avons considérés comme des essais pouvant influencer la pratique des internistes généralistes. Parmi ces articles, nous avons décidé d’en présenter cinq qui, selon nous, sont les plus pertinents en abordant des pathologies fréquemment observées dans la pratique, sont bien menés sur le plan de la méthodologie et ont le potentiel de modifier de façon durable les directives de pratique. Les références des articles qui n’ont pas été retenus figurent dans la bibliographie pour l’intérêt du lecteur. Cet article vise à présenter les cinq meilleurs articles de 2020 et à examiner leurs forces et leurs limites. Ces articles ont également fait l’objet de discussions lors de l’activité éducative virtuelle de la SCMI qui s’est tenue le 15 octobre 2020 et dans un épisode du BaladoCritique.

Keywords: COVID; Randomized Controlled Trial; lung injury
Top 5: Recovery Trial

Context
COVID-19 induces inflammatory mediated lung injury. We have no treatment to reduce mortality in hospitalized patients with COVID-19 despite high mortality rates of around 21% in hospitalized patients.\(^2\)

Clinical question: Does treatment with dexamethasone reduce 28 days mortality in hospitalized patients with COVID-19?

Methods
Design: Open label randomized controlled trial (RCT)
Setting: 176 healthcare organizations from the United Kingdoms
Population: Hospitalized patients with suspected or laboratory confirmed COVID-19. Subgroups, according to required ventilatory support were made for analysis purpose.
Intervention: The usual care plus dexamethasone 6 mg once daily (oral or intravenous) started at enrollment for up to 10 days.
Comparator: Usual care
Primary outcome: 28 days mortality
Funding source: The Medical Research Council and National Institute for Health Research and others.

Main results
This study included 6425 patients hospitalized for either suspected or confirmed COVID-19. Patients with medical history that might, in the opinion of the attending clinician, have been put at risk were excluded from the study. The participants’ mean age was 64 years and 64% were male. At randomization, 16% were under mechanical ventilation, 60% were under oxygen therapy (with or without non-invasive ventilation), and 24% were received neither. The mean duration of the treatment in dexamethasone group was 7 days. Adverse effects were not documented in the trial.

Discussion
The RECOVERY trial showed that among hospitalized patients with COVID-19, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care with a low NNT. It was pragmatic, and it addressed an important clinical question with scarce positive data so far on the matter. The large sample size provided good statistical power to this trial.

Limitations
On the flip side, the oxygen support level was not mentioned nor described in the study, making it difficult to set a specific point where the intervention is beneficial. Moreover, the exclusion criteria were not explicit and were based on clinician judgement, which may cause difficulties to generalize results in daily practice. Finally, adverse events were not specified in the trial.

Bottom line
RECOVERY is the first study to show mortality benefit among hospitalized patients for COVID-19. Mortality reduction was significant at 28 days for patient receiving either invasive ventilation or oxygen therapy. However, there was no clear benefit of dexamethasone use demonstrated among patients receiving no respiratory support. Consequently, World Health Organization (WHO) now recommends a systemic corticosteroid therapy for 7 to 10 days in patients with severe (defined by oxygen saturation <90% on room air, respiratory rate >30 breaths per minute or signs of respiratory distress) and critical COVID-19 [defined as Acute Respiratory Distress Syndrome (ARDS), sepsis or septic shock].

Table 1. 28 Days mortality

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n = 2104)</th>
<th>Usual care (n = 4321)</th>
<th>Risk ratio* (95% CI)</th>
<th>Number needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 Days mortality</td>
<td>482 (22.9%)</td>
<td>1110 (25.7%)</td>
<td>0.83 (0.75–0.93)</td>
<td>36 (20–178)</td>
</tr>
</tbody>
</table>
*Age-adjusted.

Table 2. 28 Days mortality according to respiratory support at randomization

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Usual care</th>
<th>Risk ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>95/324 (29.3%)</td>
<td>283/683 (41.4%)</td>
<td>0.64 (0.51–0.81)</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>293/1279 (23.3%)</td>
<td>682/2604 (26.2%)</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>No oxygen received</td>
<td>89/501 (17.8%)</td>
<td>145/1034 (14.0%)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
</tbody>
</table>

Data from dexamethasone in hospitalized patients with COVID-19 — Preliminary Report. The RECOVERY Collaborative Group.\(^1\)
**Top 4: Caravaggio Trial**

**Context**

Direct oral anticoagulants (DOAC) such as Rivaroxaban (SELECT-D Trial) and Edoxaban (HOKUSAI VTE Cancer Trial) are both therapeutic options for the treatment of acute venous thromboembolism (VTE) in patients with cancer. However, low molecular weight heparin (LMWH) remains the standard of care considering an increased risk of bleeding in specific sub-groups like gastrointestinal cancer.

**Clinical question:** Is treatment with Apixaban non-inferior to dalteparin (LMWH) for the prevention of recurrent venous thromboembolism in patients with cancer?

**Methods**

**Design:** Non-inferiority open label randomized controlled trial

**Setting:** 119 multinational healthcare facilities (European countries, Israel and the United States).

**Population:** Adults with cancer who had a new VTE, either pulmonary embolism or proximal deep vein thrombosis, were eligible. The cancer criteria was met if the patient had either an active cancer (diagnosis made or treatment received in the last 6 months or had a diagnosis of recurrent or metastatic cancer) or a history of cancer (diagnosis made in the last 2 years). Patients with non-melanoma skin cancer, primary or metastatic brain tumor, or acute leukemia were excluded. Patients with ECOG of 3-4, life expectancy of less than 6 months, hemoglobin less than 80 g/L or platelet count less than 75x10^9/L were also excluded.

**Intervention:** Apixaban 10 mg twice daily for the first 7 days, followed by 5 mg twice daily.

**Comparator:** Dalteparin 200 IU per kilogram of bodyweight once daily for 1 month followed by 150 IU per kilogram once daily.

**Primary outcome:** The recurrence of VTE during the 6 months trial. Major bleeding was measured as the principal safety outcome.

**Funding Source:** Bristol-Myers Squibb-Pfizer Alliance

**Main results**

1170 patients were randomized in the trial, where the mean patient age was 67.2 years in both groups. One patient out of five had an incidental discovery of their VTE disease. 97% had an active cancer, the colorectal cancer being most frequent with around 20% of the overall cases. Around 12% of participants had genitourinary cancer and 5% had upper gastrointestinal cancer. The median duration of the treatment was similar in both groups.

**Discussion**

CARAVAGGIO trial was well conducted with a large number of patients randomized in multinational healthcare facilities. The use of apixaban showed to be non-inferior to dalteparin for the prevention of recurrent VTE in patients with cancer. Moreover, sub-group analysis of primary safety outcome according to the type of cancer was highly relevant clinically, since major bleeding was higher in previous DOAC studies in patients with upper gastrointestinal (GI) or genitourinary cancer. In CARRAVAGIO trial, in opposition, there was no increase in major bleeding observed in GI malignancies like in other trials with DOAC.

**Limitations**

However, the trial had an open label design, which can induce detection bias. It was also lacking power to conclude with certainty about the absence of difference in major bleeding, which has been a concern with other DOAC. Patients with primary or metastatic brain tumor were excluded from this study although they were included in other DOAC studies, making the results less readily generalizable.

<table>
<thead>
<tr>
<th><strong>Table 3. Recurrence of VTE</strong></th>
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<tr>
<td></td>
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<tr>
<td>Recurrent VTE – no (%)</td>
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</table>

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<tr>
<th><strong>Table 4. Major bleeding</strong></th>
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<tr>
<td></td>
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<tr>
<td>Major bleeding – no (%)</td>
</tr>
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</table>

Data from Agnelli et al.
Bottom line
CARAVAGGIO trial shows the efficacy of apixaban in the prevention of recurrent VTE in patients with cancer. The trial supports the previous evidence about efficacy of DOAC for preventing VTE recurrence in patients with cancer. Although no difference between dalteparin and apixaban group was noticed about major bleedings, the study was not sufficiently powered to highlight a difference on that matter.

Top 3: Lodoco2 Trial

Context
Inflammation is known to be a part of the pathophysiology of atherosclerotic artery disease. COLCOT trial has shown that colchicine reduces the cardiovascular events in patients following a recent myocardial infarction (MI) who were revascularized. However, cardiovascular mortality and MI were not significantly reduced in that trial. LoDoCo trial, published in 2013, demonstrated a decrease in composite cardiovascular events in stable chronic and stable coronary artery disease (CAD), but the trial had methodological limitations.

Clinical question: In patients with CAD, would colchicine reduce cardiovascular events without causing harm?

Methods
Design: Double blinded randomized controlled trial
Setting: 43 healthcare facilities in Australia and Netherlands
Population: Adults from 35 to 82 years old with stable CAD. CAD had to be documented with a coronary angiography, a computed tomography angiography, or a coronary-artery calcium score of at least 400 Agatston units on a coronary-artery calcium scan. The patients’ condition had to be stable for a period of at least 6 months. Patients with moderate or severe renal impairment (creatinine >150 μmol/L or eGFR <50 ml/min), heart failure with New York Heart Association (NYHA) class 3 or 4, moderate or severe valvular heart disease, myositis, or marked sensitivity to statins were excluded from the trial.

Intervention: Colchicine 0.5 mg daily
Comparator: Placebo

Both groups, colchicine and placebo, were randomized following a month of run-in phase of colchicine 0.5 mg daily. If participants had unacceptable side effects during the run-in phase, they were excluded in the subsequent phases of the study.

Primary outcome: Composite cardiovascular events, including cardiovascular death, MI, ischemic stroke or coronary revascularization.

Funding source: National Health Medical Research Council of Australia and others.

Main results
Around 6528 patients were enrolled in the run-in phase, of which 5522 of them subsequently underwent randomization, while 611 did not because they had perceived side effects, and 395 did not because of other unspecified reasons. The mean age of patients’ was 66 years, of which 85% were male and 83% of patients had a prior coronary revascularization intervention. The period since last acute coronary syndrome was more than 24 months in 58% of patients. According to authors, the CAD was well treated, and the median follow-up of intervention was 28 months.

Discussion
LoDoCo2 trial enrolled a large number of patients and addressed the impact of colchicine on stable cardiovascular

Table 5. Cardiovascular events

<table>
<thead>
<tr>
<th>Event</th>
<th>Kolchicine (n = 2762)</th>
<th>Placebo (n = 2760)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome of cardiovascular events</td>
<td>187 (6.8%)</td>
<td>264 (9.6%)</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>83 (3.0%)</td>
<td>116 (4.2%)</td>
<td>0.70 (0.53–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>16 (0.6%)</td>
<td>24 (0.9%)</td>
<td>0.66 (0.35–1.25)</td>
<td>0.20</td>
</tr>
<tr>
<td>Ischemia-driven coronary revascularization</td>
<td>135 (4.9%)</td>
<td>177 (6.4%)</td>
<td>0.75 (0.60–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20 (0.7%)</td>
<td>25 (0.9%)</td>
<td>0.80 (0.44–1.44)</td>
<td>N/A</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>73 (2.6%)</td>
<td>60 (2.2%)</td>
<td>1.21 (0.86–1.71)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data from Nidorf et al.6
disease, which is a prevalent health issue in the general population. The ability of colchicine to decrease cardiovascular events was both statistically and clinically significant with a low NNT of 36 patients. The trial adds evidence to the clinical question that COLCOT asked previously to patients following acute MI.

**Limitations**

However, the run-in phase allowed the trial to exclude about 15% of the potential patients, mainly because of gastrointestinal side effects. It affects the external validity of the results and may underestimate the rate of side effects in practice. Finally, numerically higher mortality was observed in Colchicine group as in COPS trial, compared to placebo. None was statistically significant but neither trial had the power to show difference in mortality. It might be related to chance but being observed in two different studies might suggest an adverse effect directly related to colchicine. At this point, however, we do not have sufficient evidence or explanations to conclude on this specific point.

**Bottom line**

LoDoCo2 trial shows that Colchicine 0.5 mg daily reduces cardiovascular events in patients with stable CAD, but did not have any impact on cardiovascular mortality. The trend of increasing non-cardiovascular mortality has been observed in LoDoCo2 trial. It was not significant, but a similar trend has been observed in COPS trial, and it needs to be followed closely in the upcoming studies.

**Top 2: Voyager Pad Trial**

**Context**

Patients with peripheral artery disease (PAD) are at an increased risk of major adverse limb events (MALE) and major adverse cardiovascular effects (MACE). Patients with peripheral revascularization are at a higher risk for subsequent vascular complications. The COMPASS trial demonstrated a reduction in MALE and MACE in a broad population, including sub-group of PAD patients.  

**Clinical question:** Does treatment with rivaroxaban 2.5 mg twice a day, with aspirin, reduce a composite outcome of MALE and MACE in patients with recent revascularization for PAD?

**Methods**

**Design:** Double blinded randomized controlled trial  
**Setting:** 542 healthcare facilities in 34 countries (including Canada)  
**Population:** Adults of at least 50 years old with lower-extremity symptomatic PAD, who had undergone a successful revascularization in the past 10 days. Patients who were at increased risk of bleeding, had an acute limb ischemia within 2 weeks prior of revascularization, with an history of stroke or transient ischemic attack, had an eGFR <15 ml/min, had an or taking prohibited drug (such as clopidogrel for a period of more than 6 months) were excluded from the trial.

**Intervention:** Rivaroxaban 2.5 mg twice daily + ASA 100 mg daily  
**Comparator:** Placebo + ASA 100 mg daily

**Primary outcome:** Composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes.

**Primary safety endpoint** was major bleeding according to Thrombolysis in Myocardial Infarction (TIMI) classification.

**Funding Source:** Bayer and Janssen Pharmaceuticals

**Main results**

Around 6564 patients underwent randomization. The mean age of participants was 67 years old and 74% were male. Less than one third of patients had CAD. 65% of the patients were revascularized by endovascular procedure, while 51% had clopidogrel as part of their treatment. The median duration

<table>
<thead>
<tr>
<th>Table 6. Cardiovascular events</th>
<th>Rivaroxaban (n = 3286)</th>
<th>Placebo (n = 3278)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome of cardiovascular events</td>
<td>508 (15.5%)</td>
<td>584 (17.8%)</td>
<td>0.85 (0.76–0.96)</td>
<td>0.009</td>
</tr>
<tr>
<td>Acute limb ischemia</td>
<td>155 (4.7%)</td>
<td>227 (6.9%)</td>
<td>0.67 (0.55–0.82)</td>
<td>N/A</td>
</tr>
<tr>
<td>Major amputation for vascular causes</td>
<td>103 (3.1%)</td>
<td>115 (3.5%)</td>
<td>0.89 (0.68–1.16)</td>
<td>N/A</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>131 (4.0%)</td>
<td>148 (4.5%)</td>
<td>0.88 (0.70–1.12)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>71 (2.2%)</td>
<td>82 (2.5%)</td>
<td>0.87 (0.63–1.19)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>199 (6.1%)</td>
<td>174 (5.3%)</td>
<td>1.14 (0.93–1.40)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Clinical question: Does treatment with dapagliflozin reduce the risk of renal or cardiovascular events in patients with moderate CKD and albuminuria, with or without type 2 diabetes?

Methods

**Design**: Double blinded randomized controlled trial

**Setting**: 386 healthcare facilities in 21 countries (including Canada)

**Population**: Adults with CKD (eGFR of 25 to 75) and albumin-to-creatinine ratio (ACR) of 200 to 5000 mg/g, on a stable dose of ACEi or ARB. Minimally, 30% of the patients had to be without diabetes. Major exclusion criteria included: type 1 diabetes, polycystic kidney disease, immunotherapy for kidney disease within 6 months, and severe heart failure.

**Intervention**: Dapagliflozin 10 mg daily

**Comparator**: Placebo daily

**Primary outcome**: Composite of decline of at least 50% in eGFR, onset of end-stage kidney disease or death from renal or cardiovascular causes.

**Funding source**: Astra Zeneca

Main results

Around 4304 patients underwent randomization. The mean age of participants was 62 years and 67% were male, and 2 patients out of 3 had type 2 diabetes, and 37% had cardiovascular disease. On average, initial patients’ eGFR was 43 ml/min in both groups and median ACR was 95 mg/g. Nearly 98% of the patients were treated with either ACEi or ARB when randomized in the trial. Median follow-up took place for 2.4 years, but the trial was prematurely interrupted because of positive results. Discontinuation of treatment due to adverse events was similar in both groups, including ketoacidosis and amputation.

Discussion

VOYAGER-PAD was a large trial that aimed to answer a clinical question on which the literature was minimal to date. The trial methodology was strong, and it demonstrated a statistical and clinical benefit on composite outcome including MALE, which has a major impact on patients’ quality of life. The NNT was 43.

Limitations

On the flip side, an increase in major bleeding was observed. Also, the exclusion criteria “increased risk of bleeding” did not have a specific definition, and relied mostly on the clinician’s judgment. Consequently, the risks-benefits balance of rivaroxaban treatment might be hard to transpose to various medical situations faced by clinicians. Finally, no data are available on the measured outcomes, following an initial 28 months follow-up.

Bottom line

The VOYAGER-PAD trial shows that Rivaroxaban 2.5 mg twice daily with aspirin reduces a composite of MALE and MACE in patients with PAD who undergo revascularization. It is the first RCT to show a reduction of this outcome. VOYAGER-PAD complements data from COMPASS trial in patients with PAD. However, the risk of bleeding is probably increased in this population, and thus, the potential benefits of rivaroxaban must certainly be weighed against the risk of bleeding when initiated.

Top 1: DAPA-CKD Trial

Context

Only Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARB) have been shown to slow decline in kidney function in patients with chronic kidney disease (CKD). Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have demonstrated benefits on cardiovascular and renal outcomes in patients with diabetic nephropathy, as stated in CREDENCE trial.

Table 7. Major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n = 3286)</th>
<th>Placebo (n = 3278)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major bleeding</td>
<td>62 (1.90%)</td>
<td>44 (1.35%)</td>
<td>1.43 (0.97–2.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>140 (4.30%)</td>
<td>100 (3.08%)</td>
<td>1.42 (1.10–1.84)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data from Bonaca et al.

Clinical question: Does treatment with dapagliflozin reduce the risk of renal or cardiovascular events in patients with moderate CKD and albuminuria, with or without type 2 diabetes?
emphasized the clinical benefit of the intervention which was added on top of ACEi and ARB. Furthermore, the benefits in renal and cardiovascular events observed in Dapagliflozin group, were present both in patients with and without type 2 diabetes. Also, Dapagliflozin administration tends to show a similar effect on eGFR than ACEi and ARB: an initial drop when the medication is introduced, but a lower rhythm of decline over time.

Limitations
On the other hand, the study was interrupted prematurely, which can overestimate the magnitude of differences between groups. Also, early interruption of the trial induced a shorter than expected follow-up, which remains relatively short at 2.4 years for a condition having a long-term evolution. Also, many exclusion criteria were specified, which may lower the ability of physicians to generalize the results to their patients.

Bottom line
The DAPA-CKD trial showed that dapagliflozin lower the risk of the primary composite outcome of a sustained decline in eGFR of at least 50%, end-stage kidney disease or death from renal or cardiovascular causes in patients with CKD and albuminuria with or without diabetes. It confirms the CREDENCE trial results, but in a broader CKD population.

Statement of the Contributions of the Authors
G.H. carried out the literature search to find the Top 5 papers, contributed to the analysis and discussion of selected papers, and reviewed the original manuscript of this article.

O. S-L contributed to the analysis and discussion of selected papers and wrote the original manuscript of this article.

Statement of Conflict of Interests
G.H. received honoraria to participate to a Bayer’s advisory board last year.

O. S-L has no conflict of interest.

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