

2021

## Conjugated estrogen is an effective option to manage chronic GI bleeding in a patient with atrial fibrillation and end-stage renal disease

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### Recommended Citation

COMPTON MT, PATEL K. Conjugated estrogen is an effective option to manage chronic GI bleeding in a patient with atrial fibrillation and end-stage renal disease. *Clin. Res. Prac.* Jun 29 2021;7(1):eP2753.  
<https://doi.org/10.22237/crp/1622160660>

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### Cover Page Footnote

Acknowledgement: The authors would like to acknowledge Dr. James Meza for his editorial support in preparation of this manuscript.

# Conjugated estrogen is an effective option to manage chronic GI bleeding in a patient with atrial fibrillation and end-stage renal disease

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**ABSTRACT** A clinical decision report using:

Livio M, Mannucci PM, Viganò G, Mingardi G, Lombardi R, Mecca G, Remuzzi G. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med*. 1986;315:731-735 <https://doi.org/10.1056/NEJM198609183151204>

for a patient with chronic GI bleeding and complicated pro- and anti-coagulation needs.

**Keywords:** *conjugated estrogen, bleeding, renal disease, atrial fibrillation, hormonal therapy*

## Clinical-Social Context

Charlotte Cunningham [pseudonym] is a 66-year-old woman who presented to the Emergency Department with melena and dyspnea. She has a significant past medical history for atrial fibrillation controlled with warfarin, end-stage renal disease (ESRD) receiving dialysis and erythropoietin (EPO) three times per week, congestive heart failure, hypertension, and coronary artery disease (CAD) with dual anti-platelet therapy (DAPT) due to stent placement one month before presentation.

Mrs. Cunningham has a 5-month history of gastrointestinal (GI) bleeding and received multiple esophagogastroduodenoscopies (EGDs) and colonoscopies to determine the source of her bleeding. When none of those endoscopies were able to determine a source, a capsule endoscopy was performed which was also unable to pinpoint a site of bleeding. During her complicated 2-week hospital stay, she received multiple RBC transfusions due to dropping hemoglobin levels despite receiving EPO three times per week. This was further complicated by her need for long-term anti-coagulation due to her history of atrial fibrillation and dual anti-platelet therapy due to CAD with recent stent placement. To determine a cause of her GI bleeding, we performed a tagged RBC scan which showed some small sites of bleeding but nothing large enough to cause the amount of blood loss that was present during the current admission.

Although Mrs. Cunningham was worried that we were unable to locate a source of bleeding, she was happy that someone was going to investigate options to control her blood loss; she hoped this would prevent the need for further blood transfusions, which was her greatest concern. Mrs. Cunningham also expressed that her supportive

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ISSN: 2379-4550

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husband has helped manage her many medical problems at home, and he often takes the responsibility for her care, including transportation to dialysis. She shared her wish to find a solution, so she could be less of a caregiver burden and financial stressor to him. More than anything, Mrs. Cunningham wanted her husband to enjoy his life as he was relatively healthy in comparison to her situation.

The cardiology consultant was very concerned with clot formation and re-obstruction of the stent and insisted that DAPT be continued. As the primary care team, we ordered every test at our disposal to determine a location of the blood loss but were unable to identify a treatable source of her bleeding. This required the internal medicine team to brainstorm different treatments that could be used to balance the patient's pro and anti-coagulation needs. Since she was already taking EPO without improvement, the team challenged themselves to find a long-term solution that would balance the competing needs for this patient. The resulting discussions allowed the clinical decision making to become observable as many possible therapeutic options were considered. Most options were too short-lived or counteracted by the anti-coagulants.

The internal medicine team suggested the use of conjugated estrogens to use their associated hypercoagulability effects to provide long-term (2-4 weeks) pro-coagulation. This would reduce her GI bleeding and the need and risk of chronic blood transfusions, without interfering too severely with her need for anti-coagulation. While it has been used to treat platelet dysfunction seen in patients on hemodialysis<sup>2</sup>, the team wondered about the efficacy of this treatment for our patient.

## Clinical Question

Is conjugated estrogen an effective treatment for chronic GI bleeding for a patient with ESRD?

## Research Article

Livio M, Mannucci PM, Viganò G, Mingardi G, Lombardi R, Mecca G, Remuzzi G. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med.* 1986;315:731-735 <https://doi.org/10.1056/NEJM198609183151204>

## Description of Related Literature

A literature review using PubMed Advanced Search was performed using the key words (Conjugated estrogen) AND (bleeding) AND (renal disease) and sorted by best match. Twenty eight articles were found and then reviewed for their relevance to the clinical question. All case reports were removed from further consideration. Review articles were reviewed for further relevant articles. This resulted in four relevant articles for further review.

Shemin et al. assessed four patients with chronic renal failure, prolonged bleeding time, and clinical bleeding given conjugated estrogen vs. five patients treated with placebo. However, this study had a small sample size, making it of limited value to answer the clinical question.<sup>1</sup>

Lewis et al. is a cohort study measuring the efficacy of daily hormonal therapy in bleeding from small bowel angiodysplasia; however, this study was not blinded and its strong potential for bias also excluded it from being chosen.<sup>2</sup>

Heisteringer et al. is a randomized placebo-controlled, double-blind crossover study investigating the effect on conjugated estrogens on bleeding in seven patients with ESRD.<sup>3</sup> All seven patients given conjugated estrogens for five days showed a statistically significant reduction of bleeding time on days 7 and 14, with reduced effects on day 21 and no remaining effects on day 28. This study was completed on patients with ESRD receiving hemodialysis which fits our study population. The subjects were also used as their own controls, however, the study excluded patients with comorbid conditions, such as our patient, limiting the usefulness of applying the data to our clinical scenario.



A randomized, double-blind, placebo-controlled crossover study by Livio et al., investigating the efficacy of intravenous conjugated estrogens in shortening the prolonged bleeding time in six patients on hemodialysis with bleeding tendencies was chosen for further critical appraisal. Patients given conjugated estrogen had a reduced bleeding time from hour 6 after administration to day 21 as compared to themselves taking a placebo treatment. The methodology of this study was superior compared to the previous reviewed articles. The study was double blinded to reduce researcher bias, had 100% compliance at the conclusion of the study (although with very few cases), and used subjects that fit our patient profile without excluding any comorbid conditions seen in our patient.<sup>4</sup>

The Grade of Recommendation for conjugated estrogens to address bleeding problems in clinical practice is B, based on few, lower quality studies.<sup>5</sup>

## Critical Appraisal

Livio et al. was a randomized, double-blinded, placebo-controlled crossover study at the renal unit from a hospital in Milan looking at a total of six patients. All patients in the study were admitted based on concomitant chronic renal failure and a history of bleeding with documented prolonged bleeding time. Clinically, the bleeding events were menorrhagia (1), epistaxis (3), and gingival bleeding (2). The study evaluated the efficacy of conjugated estrogen to reduce bleeding time in uremic patients who were undergoing regular hemodialysis. None of the patients received blood transfusions or blood products for three months preceding the study nor had they taken aspirin or other platelet drugs within twenty days of the trial. Notably, these patients differed in this way from our patient. Also, a disease-oriented outcome—bleeding time—was the primary outcome measure. However, the authors did report clinical outcomes related to bleeding conditions, which adds to the utility of this study to assist with decision making.

The patients were randomly assigned using a double-blinded method to receive IV infusions of conjugated estrogen or a placebo and then crossed over to the other treatment after one month. Patients were given either the placebo or cumulative doses of conjugated estrogen to induce rapid onset of action for 6-10 days starting 24 hours after the end of the previous dialysis session. Multiple parameters were measured at hours 0, 6, 24, 48, 72, and 96 after beginning infusion which included: bleeding time, factor VIII coagulation activity, von Willebrand factor (vWF) antigen, ristocetin cofactor, platelet retention, and serum thromboxane B2. Bleeding time was measured at days 7, 14, 21, and 30 after the start of treatment.

To evaluate the efficacy of conjugated estrogens for use in reducing the bleeding time, researchers analyzed properties of factor VIII and vWF using one-way analysis of variance. Bleeding times were compared using the Friedman test with a non-normal distribution. All remaining parameters were analyzed using Student's t-test with paired data. No significant changes were noted in most of the analyzed parameters; however, all patients treated with conjugated estrogen showed a reduction in bleeding time starting at hour 6, peaking around day 5 to 7, and returning to baseline between days 16-25. Patients who were actively hemorrhaging stopped within 48 hours of administration of conjugated estrogens, which was confirmed by stabilization of their hematocrit. There were results that the authors did not report for reasons that were not explained.

Several conclusions were drawn from this study with the most relevant to our clinical question being that conjugated estrogen was effective at reducing bleeding time and stopping active hemorrhages. The study concluded that conjugated estrogen reduced the bleeding time in uremic patients compared to the placebo and had more of a long-term effect (at least 2 weeks) compared to the relatively short acting effects of desmopressin (4 hours) and cryoprecipitate (12-18 hours). While conjugated estrogen is an option for treatment of chronic bleeding in uremic patients, desmopressin and cryoprecipitate are more effective when immediate control of the bleeding time is necessary.

The design of a double-blinded randomized crossover study eliminates biases associated with patients and researchers. A crossover study allows a patient to be their own control group, thereby, eliminating sources of confounding variables. The infusions were given in 50ml of normal saline in a blinded fashion, which makes the treatments look identical and minimizes any procedural bias. The study had 100% retention, which prevents any attrition bias. There are no disclosures, which may indicate funding or publication bias since it was funded by a grant from the Italian National Research Council. The study was also compared to a placebo, which allowed for analysis of the benefit of conjugated estrogens compared to no treatment. However, there were limitations of the study in that there was a very small sample size, which limits conclusions that can be made about the general population.



The population of the study did correlate adequately to our patient because it included patients with multiple comorbidities, such as hypertension and coronary artery disease, both of which are seen in our patient. It also specifically analyzed patients with chronic renal failure on hemodialysis with increased bleeding times. Some limitations of the patient population are that the study was predominantly male (66%), and the average age was 41 which is significantly lower than our patient's age of 66-years-old. While the study did include a wide range of bleeding histories, such as epistaxis, menorrhagia, and gingival bleeding, none of the patients who were included in the study had a history of chronic GI bleeding.

According to the SORT criteria, the quality of this publication is Level 2 based on patient-oriented evidence and sound methodology, but limited case numbers.

## Clinical Application

Livio et al. concluded that conjugated estrogens are effective at reducing the bleeding time in uremic patients and has a longer duration of action than the standard treatments of desmopressin and cryoprecipitate. For patients with chronic bleeding, conjugated estrogen may be used for longer duration bleeding control as required by our patient Mrs. Cunningham.

Conjugated estrogens are a viable option to address the concerns that Mrs. Cunningham brought up to the internal medicine team. It could provide a means to control her chronic GI bleeding while still maintaining an adequate level of anti-coagulation, which would reduce her need for future hospitalizations and chronic blood transfusions. This would go a long way in reducing the burden and financial stressor she feels that her condition places on her husband; it would also give her a much-needed sense of independence back. Upon discussing this option with Mrs. Cunningham, she agreed to try the conjugated estrogen and follow up closely for monitoring of her lab values to determine adequate therapeutic range and efficacy. Completely unaddressed is the fact that Livio, et al. used intravenous conjugated estrogens, where it would be more practical for our patient to use an oral formulation. This level of application of the study findings required more coordination of care from inpatient to outpatient settings for our patient.

There is low risk of harm in the use of conjugated estrogens for the control of chronic bleeding. The low dose of conjugated estrogen used for management (0.6 mg/kg/day) reduces the chance of side effects with the most reported effect being hot flashes. Thrombogenic risks are part of the clinical scenario and less associated with the therapy itself. Livio et al. recorded no complications of significant adverse effects from any of the six patients studied.

## New Knowledge Related to Clinical Decision Science

In clinical practice, there are occasions when there is no clear best approach and different options each have drawbacks or risks. This patient had contradictory and concomitant problems with risks of both bleeding and clotting complications (GI bleeding versus atrial fibrillation and stroke). This is not an uncommon problem found in clinical practice; it is also especially evident among geriatric populations as they often have multiple comorbidities that aren't directly met in inclusion criteria for most clinical research. In these situations, clinical experience or prior patient care may influence the clinical decision.

Often, clinicians look for an excuse in a post hoc manner to justify a decision they are comfortable making. This passive decision-making and unspoken rationale are things doctors need to try to avoid. It is better to clearly state the risk of benefit and the risk of harm while explaining a patient-centered clinical decision. In this case, the platelet dysfunction associated with end-stage renal disease has an additive effect to whatever platelet dysfunction is generated by iatrogenic antiplatelet therapy for the coronary artery disease. Yet, this is in the setting of obvious problems with bleeding. Given the inherent risks, the attitudes, fears, and risk tolerance of the treating physicians also cannot be ignored. It is up to the physician to understand when this treatment should be recommended, and which patient population would be eligible and most suited. It is also a physician's job to make sure the treatment won't cause any unfavorable side effects, and any such should be discussed with the patient before starting the medication. This clinical decision report provides an example of clinicians working together and brainstorming possible management options. Specifically, the brainstorming for a therapy not based on implicit recommendations is clinical decision science in action.



Furthermore, the fact that there is some clinical research literature available provides some confidence and reassurance for both the treating physicians as well as the patient.

## Conflict Of Interest Statement

The author declares no conflicts of interest.

## Acknowledgement

The authors would like to acknowledge Dr. James Meza for his editorial support in preparation of this manuscript.

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