

IPR2023-01064 – Patent 11,400,063

MURRAY & POOLE ENTERPRISES LTD. (“M&P”),
Petitioner

v.

INSTITUT DE CARDIOLOGIE DE MONTREAL (“MHI”),
Patent Owner

Murray & Poole’s Demonstrative Exhibits

Oral Argument

October 15, 2024

IPR2023-01064
M&P v. MHI
M&P Ex. 1082



BIOPHARMA LAW GROUP PLLC

Solutions for Life Science Innovation

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



Agenda

- Background
- Ground 2
 - EX1006 Is Prior Art
 - EX1006 Discloses All Claim Limitations
- Ground 3
 - All Claim Limitations Taught Except TTI “within about 3 days of MI”
 - “Without pre-loading”
 - Following PCI



Agenda

- Ground 3 cont'd
 - Motivation to Reduce TTI to “within about 3 days”
 - Trend in the art to reduce TTI
 - Routine optimization
 - In view of ESC Guidelines
 - Reasonable expectation of success
 - No hindsight, teaching away, or unpredictability
- No Objective Indicia
- Grounds 1 and 4
 - No Entitlement to 2019 Provisional Filing Date
 - TTI Periods in EX1005 are “By Another”
- Motion to Exclude



Background - Colchicine

- Centuries old anti-inflammatory drug
- 2009: Received FDA approval as COLCRYS® (EX1016)
- Indications: Gout and familial Mediterranean fever (FMF)
- Dosage:
 - Gout flares
 - Prophylaxis of gout flares: max 1.2 mg/day
 - Treatment of gout flares: 1.2 mg at first sign of flare followed by 0.6 mg one hr later
 - FMF: max 2.4 mg/day

COLCRYS™ (colchicine, USP) tablets for Oral use**Initial U.S. Approval: 1961****INDICATIONS AND USAGE**

COLCRYS (colchicine, USP) tablets are an alkaloid indicated for

- gout flares (1.1)
- Familial Mediterranean fever (FMF) in adults and children 4 years or older (1.2).

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION

- **Gout Flares:** 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later (2.1).
- **FMF:** Adults and Children older than 12 years 1.2 – 2.4 mg; Children 6 to 12 years 0.9 – 1.8 mg; Children 4 to 6 years 0.3 – 1.8 mg. (2.2, 2.3).
 - Give total daily dose in one or two divided doses (2.2).
 - Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose (2.4).
- See full prescribing information for dose adjustment regarding patients with impaired renal function (2.5) or hepatic function (2.6).

DOSAGE FORMS AND STRENGTHS

- 0.6 mg tablets (3).

CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors (5.3). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses (7).

WARNINGS AND PRECAUTIONS

- *Fatal overdoses* have been reported with colchicine in adults and children. Keep COLCRYS out of the reach of children (5.1, 10).
- *Blood dyscrasias:* myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported.
- Monitor for toxicity and if present consider temporary interruption or discontinuation of colchicine (5.2, 5.3, 5.4, 6, 10).
- *Drug interaction P-gp and/or CYP3A4 inhibitors:* Coadministration with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death (5.3, 7).
- *Neuromuscular toxicity:* Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to cause this effect. Consider temporary interruption or discontinuation of COLCRYS. (5.4, 7).

Background – LoDoCo 2013

- **LoDoCo (Low-Dose Colchicine) Trial Overview (EX1007, EX1020)**
 - **Objective:** Tested the efficacy and safety of low-dose colchicine in preventing cardiovascular events in patients with stable coronary artery disease (CAD)
 - **Intervention:** 0.5 mg once daily colchicine
 - **Results:** Reduction in cardiovascular event is acute coronary syndrome (Acute Myocardial Infarction or Unstable Angina), out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke.
- **LoDoCo2 Trial (EX2065, August 2020) – placebo controlled, confirmed the results of LoDoCo**
- **LODOCO®**, owned by Petitioner, approved by FDA in June 2023

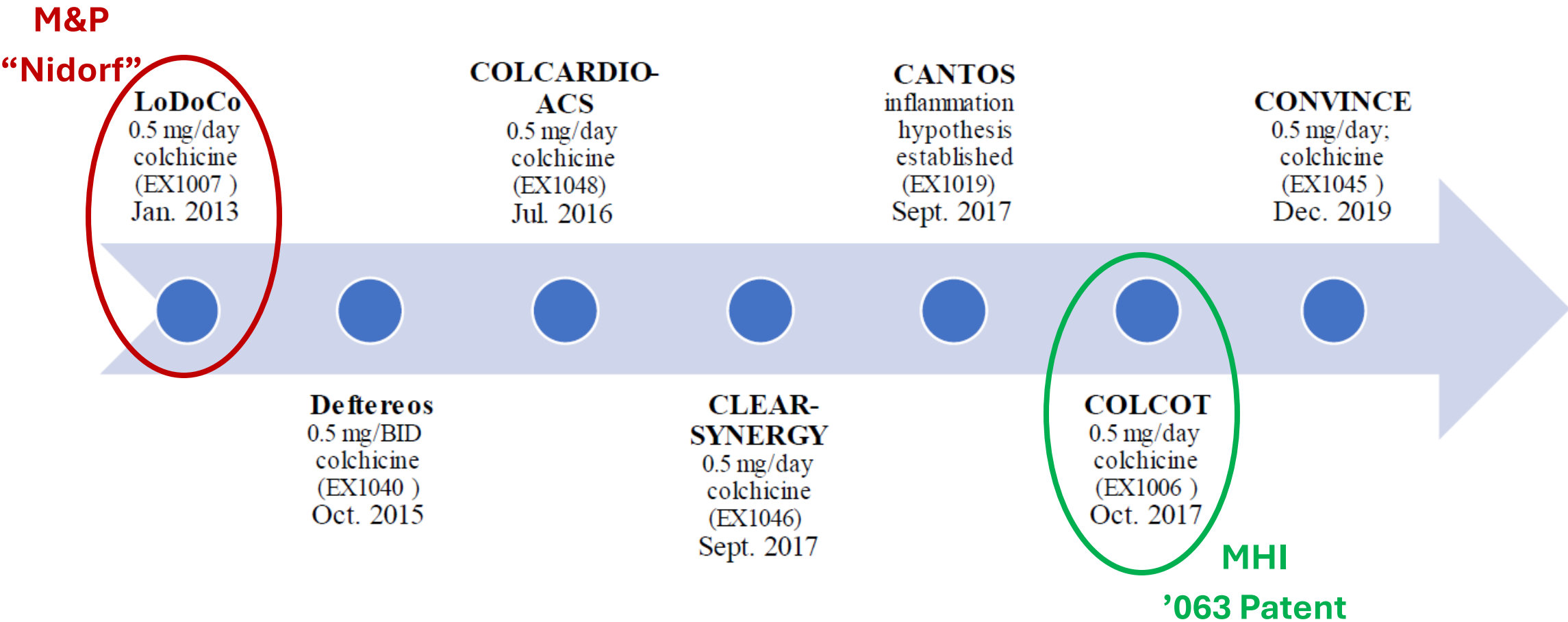


Background – CANTOS 2017

- **CANTOS** (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) clinical trial
 - **Objective:** Test whether reducing inflammation with canakinumab, **without affecting cholesterol levels**, lowers risk of recurrent cardiovascular events in patients with history of MI
 - Canakinumab: monoclonal antibody targeting interleukin-1 β (IL-1 β), a pro-inflammatory cytokine
 - **Dosage:** Canakinumab at 50mg/150 mg/300 mg, or a placebo
 - **Patient Population:** **at least 30 days** post-MI
 - **Results:** Canakinumab 150 mg dose significantly reduced recurrent cardiovascular events compared to placebo (**published** August 27, 2017, EX1019)
- Targeting inflammatory pathway in post-MI patients significantly lowered rate of recurrent cardiovascular events: nonfatal MI, nonfatal stroke, cardiovascular death
- Same inflammatory pathway is associated with colchicine in therapy of chronic atherosclerosis.



Background



Background – COLCOT 2019

- **COLCOT (Colchicine Cardiovascular Outcomes Trial) Overview**
 - **Objective:** Tested whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after MI (myocardial infarction)
 - **Intervention:** 0.5 mg once daily colchicine or placebo
 - **Patient Population:** Within 30 days of MI
 - **Results:** Reduction in occurrence of major adverse cardiovascular events, which included cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, and urgent hospitalization for angina leading to coronary revascularization.
 - **Published online November 16, 2019 (EX1022).**

Background - EX1005

- *Post hoc* analysis in Bouabdallaoui (EX1005)
 - Published online **August 29, 2020**
 - Time-to-treatment initiation (TTI): 0-3 days, 4-7 days, 8-30 days
 - Source of information for '063 patent claims



ESC
European Society
of Cardiology

European Heart Journal (2020) 41, 4092–4099
doi:10.1093/eurheartj/ehaa659

FAST TRACK CONGRESS
Intensive cardiac care and acute coronary syndromes

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)

Nadia Bouabdallaoui ¹, **Jean-Claude Tardif** ^{1*}, **David D. Waters** ²,
Fausto J. Pinto ³, **Aldo P. Maggioni**⁴, **Rafael Diaz**⁵, **Colin Berry** ⁶,
Wolfgang Koenig^{7,8,9}, **Jose Lopez-Sendon**¹⁰, **Habib Gamra**¹¹, **Ghassan S. Kiwan**¹²,
Lucie Blondeau ¹³, **Andreas Orfanos** ¹³, **Reda Ibrahim**¹, **Jean C. Grégoire**¹,
Marie-Pierre Dubé¹, **Michelle Samuel**¹, **Olivier Morel**^{14,15}, **Pascal Lim**¹⁶,
Olivier F. Bertrand¹⁷, **Simon Kouz**¹⁸, **Marie-Claude Guertin**¹³, **Philippe L. L'Allier**¹,
and Francois Roubille ¹⁹



Background

(12) **United States Patent Tardif**

(10) **Patent No.:** US 11,400,063 B2
(45) **Date of Patent:** Aug. 2, 2022

(54) **EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION**

(71) Applicant: **INSTITUT DE CARDIOLOGIE DE MONTREAL**, Montreal (CA)

(72) Inventor: **Jean-Claude Tardif**, Montreal (CA)

(73) Assignee: **INSTITUT DE CARDIOLOGIE DE MONTREAL**, Montreal (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/097,285**

(22) Filed: **Nov. 13, 2020**

(65) **Prior Publication Data**
US 2021/0145773 A1 May 20, 2021

Related U.S. Application Data
(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.

(51) **Int. Cl.**
A61K 31/165 (2006.01)
A61P 9/10 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/165** (2013.01); **A61P 9/10** (2018.01)

(58) **Field of Classification Search**
CPC **A61K 31/165**
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS
10,265,281 B2 4/2019 Nidorf

FOREIGN PATENT DOCUMENTS
WO WO-2014/066944 A1 5/2014

OTHER PUBLICATIONS

Akodad et al., "Interest of colchicine in the treatment of acute myocardial infarct responsible for heart failure in a mouse model," *Int J Cardiol.* 240:347-353 (2017).
Bouabdallaoui et al., "Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)," *Eur Heart J.* 00:1-8 (2020).
Deftereos et al., "Anti-Inflammatory Treatment with Colchicine in Acute Myocardial Infarction: A Pilot Study," *Circulation* 132(15):1395-403 (2015).
Hennessy et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction," *Am Heart J.* 215:62-69 (2019).
Newby et al., "Inflammation as a Treatment Target after Acute Myocardial Infarction," *N Engl J Med.* 381(26):2562-2563 (2019).
Nidorf et al., "Low-dose colchicine for secondary prevention of cardiovascular disease," *J Am Coll Cardiol.* 61 (4):404-410 (2013).
Nidorf et al., "Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview," *Clin Ther.* 41(1):41-48 (2019).
Tardif et al., "Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction," *N Engl J Med.* 381(26):2497-2505 (2019).
Tucker et al., "Colchicine as a Novel Therapy for Suppressing Chemokine Production in Patients with an Acute Coronary Syndrome: A Pilot Study," *Clin Ther.* 41(10):2172-2181 (2019).
Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: ACT Coronary Angiography Study," *JACC Cardiovasc Imaging.* 11 (2 PT 2):305-316 (2018).
Vaidya et al., "The Role of Colchicine in Acute Coronary Syndromes," *Clin Ther.* 41 (1): 11-20 (2018).
Office Action for Canadian Patent Application No. 3,099,143 dated Mar. 5, 2021 (6 pages).
Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT)," U.S. National Library of Medicine, NCT02551094, dated Sep. 16, 2015 (9 pages).
Office Action for Canadian Patent Application No. 3,099,143 dated Sep. 16, 2021 (4 pages).

Primary Examiner — Brian J Davis
(74) **Attorney, Agent, or Firm** — Clark & Elbing LLP

(57) **ABSTRACT**
The invention relates to colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method including initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

50 Claims, 3 Drawing Sheets

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

8. A method of treating a patient alter having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

27. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.



Background

(12) **United States Patent Tardif**

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50 Claims, 3 Drawing Sheets

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8. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

27. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.



Background

Ground	Claims	Basis	References
1	1-13, 17-26, 28, 40-46, 49, 50	§ 102	Bouabdallaoui
2	27, 29-36, 39	§ 102	COLCOT Protocol
3	1-50	§ 103	Nidorf in view of COLCOT Protocol, ESC Guidelines, and COLCRYS
4	1-26, 28, 40-50	§ 103	Bouabdallaoui in view of COLCRYS



Ground 2

Ground	Claims	Basis	References
1	1-13, 17-26, 28, 40-46, 49, 50	§ 102	Bouabdallaoui
2	27, 29-36, 39	§ 102	COLCOT Protocol
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4	1-26, 28, 40-50	§ 103	Bouabdallaoui in view of COLCRYS

Ground 2

27. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

Ground 2

- COLCOT Protocol (EX1006) was a publicly accessible printed publication in time to be prior art to the '063 Patent.
- Claim only requires one active step of “**initiating** the administration of colchicine...”
- “Reducing the risk of stroke”
 - Should be construed as **non-limiting**.
 - Even if limiting, **COLCOT Protocol inherently** discloses this effect.
 - **Known from LoDoCo** that colchicine reduces risk of stroke.
- **Institution Decision got this right** and MHI has not demonstrated that this claim should be construed differently.

<https://web.archive.org/web/20171020004013/https://clinicaltrials.gov/ct2/show/NCT02551094>

Go

SEP 20 OCT 20 MAY 2019

22 captures

30 Oct 2017 - 9 Dec 2022

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NIH U.S. National Library of Medicine

ClinicalTrials.gov

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 Saved Studies (0)

Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)

This study is currently recruiting participants.

See [Contacts and Locations](#)

Verified March 2017 by Montreal Heart Institute

Sponsor: Montreal Heart Institute

⚠

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

Information provided by (Responsible Party): Montreal Heart Institute

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

▶ Purpose

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Page 1 of 7

MURRAY & POOLE EXHIBIT 1006

- COLCOT Protocol (EX1006)
- Discloses all claim 27 limitations
- In time to be prior art to the '063 Patent.
- Publicly accessible **March 8, 2017**

▶ Purpose

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

EX1006 at 1; Pet. (Paper 1) at 29-32.

EX1082
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



Ground 2

Detailed Description:

Atherosclerosis is the most common cause of myocardial infarction, stroke and peripheral arterial disease. Research has clearly demonstrated that inflammation plays a key role in the initiation, progression and manifestations of atherosclerosis. Atherosclerotic lesions begin as an accumulation of lipid-laden cells (primarily macrophages) beneath the endothelium, and progress with the further accumulation of cells, connective-tissue elements, lipids and debris through immunological and inflammatory activation. Neutrophils and other inflammatory cells have been shown to invade culprit atherosclerotic lesions in acute coronary syndromes. It is likely that the inflammatory process is responsible for the high rate of cardiovascular events despite significant advances in the treatment of risk factors such as hypercholesterolemia and hypertension. It is vital to improve our understanding of the inflammatory nature of atherosclerotic disease and modify the inflammatory process with targeted therapies. Prospective cohort studies have consistently shown that high sensitivity C-reactive protein (hs-CRP) and several other biomarkers of inflammation are independently associated with increasing risk of future cardiovascular events in different populations. This together with animal models showing that reduced inflammation has anti-atherosclerotic effects, create the impetus to test the hypothesis that treatment of the underlying inflammatory process will contribute to improved cardiovascular clinical outcomes. Colchicine is an inexpensive, yet potent, anti-inflammatory drug approved for acute use in patients with gout and chronic use in patients with Familial Mediterranean Fever. The mechanism of action is through the inhibition of tubulin polymerization and potentially also through effects on cellular adhesion molecules and inflammatory chemokines. Colchicine may also have direct anti-inflammatory effects by inhibiting key inflammatory signaling networks known as the inflammasome and pro-inflammatory cytokines. Through the disruption of the cytoskeleton, colchicine is believed to suppress secretion of cytokines and chemokines as well as in vitro platelet aggregation. Considerable work has highlighted the potential of colchicine in the treatment of cardiovascular diseases mediated by pro-inflammatory processes. More recently colchicine has been evaluated for its effect on cardiovascular events in patients with coronary artery disease (CAD).

EX1082



Ground 2

Primary Outcome Measures:

- Cardiovascular death [Time Frame: approximately 3 to 4 years]
number of days from randomization
- resuscitated cardiac arrest [Time Frame: approximately 3 to 4 years]
number of days from randomization
- acute myocardial infarction [Time Frame: approximately 3 to 4 years]
number of days from randomization
- stroke [Time Frame: approximately 3 to 4 years]
number of days from randomization
- hospitalization for angina requiring coronary revascularization [Time Frame: approximately 3 to 4 years]
number of days from randomization

- Nidorf patent (EX1007) already taught reduction of stroke when treated with colchicine.

The table below shows primary outcome (i.e., cardiovascular event such as acute coronary syndrome, out-of-hospital cardiac arrest or noncardioembolic ischemic stroke) in patients receiving at least one antithrombotic agent, such as aspirin, clopidogrel or warfarin. Most patients also received additional medical such as beta blockers, statins, etc. As seen in the data, a primary outcome was less in patients receiving colchicine and at least one antithrombotic agent (4.5%) than in patients receiving at least one antithrombotic agent but not colchicine (16%). Moreover, primary outcome was less in patients receiving colchicine and at least aspirin (4.67%) than in patients receiving at least aspirin but no colchicine (14.7%). In other words, the addition of colchicine to patients receiving at least one antithrombotic agent, such as aspirin, further reduces the incidence of a primary outcome such as acute coronary syndrome, fatal or non-fatal out of hospital cardiac arrest or non-cardio-embolic ischemic stroke.

EX1007, col. 21, lines 5-22

This trial demonstrates that the addition of colchicine 0.5 mg/day to standard therapy in patients with stable coronary disease significantly reduces the risk of a cardiovascular event, including an ACS, out of hospital cardiac arrest and non-cardio-embolic ischemic stroke. The benefits of colchicine were achieved on a background of widespread use of effective secondary prevention strategies, including high dose statins, as evidenced by the low event rate in the control group. The effect of adding colchicine became evident early, continued to accrue over time and was largely driven by a reduction in ACS unrelated to stent disease.

EX1007, col. 21, lines 55-59



Ground 3

Ground	Claims	Basis	References
1	1-13, 17-26, 28, 40-46, 49, 50	§ 102	Bouabdallaoui
2	27, 29-36, 39	§ 102	COLCOT Protocol
3	1-50	§ 103	Nidorf in view of COLCOT Protocol, ESC Guidelines, and COLCRYST
4	1-26, 28, 40-50	§ 103	Bouabdallaoui in view of COLCRYST

Ground 3

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

8. A method of treating a patient alter having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.



Ground 3

Independent claims 1 and 8	Nidorf	COLCOT Protocol	ECS Guidelines
1[a], 8[a]: A method of treating a patient after having a myocardial infarction (MI) ,	✓	✓	
1[b], 8[b]: the method comprising initiating the administration of colchicine at a daily low dose to the patient,	✓	✓	
1[c], 8[c]: wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose,	✓	✓	
1[d], 8[d]: within about 3 days of the MI	After CAD (including MI) has been stable for 6 months	Within 30 days of MI	Recommending initiating treatment early during the 2-3 days of hospital stay
1[e] wherein percutaneous coronary intervention was performed for treating the patient's MI.	✓	✓	
8[e] wherein the patient is at a lower risk of a cardiovascular event... , and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.	✓	✓	



Ground 3

- All Claim Limitations Taught by Nidorf and COLCOT Except TTI “within about 3 days of MI”
 - “Without pre-loading”
 - Following PCI
- There was motivation to reduce TTI to “within about 3 days of MI”
 - Not a big leap since many studies already showed earlier TTI, including Hennessy cited during prosecution which admitted patients “if they had sustained a type 1 acute MI (by the 3rd universal definition[]) within the prior 7 days.” EX1028 at 2.
- Only new evidence from MHI is providing several new articles often ***without pin-point citations*** to allege hindsight, teaching away, or unpredictability.
- Institution Decision concluded correctly and MHI has not produced any new, credible evidence to suggest otherwise.

Ground 3 – “Without Pre-Loading”

- LoDoCo (EX1007) taught with and without pre-loading
- If preloading was intended, it would have been **expressly** stated
 - Silence about preloading ≠ loading dose
 - According to Dr. Ridker, if silence meant loading dose, patient care could be jeopardized. Dr. Ardehali agreed.

49. I disagree. A POSA would understand that a loading dose of the active ingredient being studied in a clinical trial such as the ones reported in Nidorf and Bouabdallaoui would be expressly stated if it were to be administered, and that the absence of any mention of a loading dose of the active ingredient being studied means that no loading does should be administered. Because dosing errors are so commonly made and can be so dangerous, physicians are trained to be explicit when they talk about dose requirements to their patients as well as in all written documents, including clinical trial protocols and results. Had the authors wanted a loading dose to be given, they would have absolutely stated so.



Ground 3 – “Without Pre-Loading”

9 Q. If a medication is not understood to have
10 been tested with a loading dose, would you just add
11 a loading dose on your own?

12 A. No. I mean, the majority of the medications
13 we give to our patients is one dose, and you just
14 give it to your patients and, you know, to make sure
15 that the therapeutic effect of the drug is within
16 the therapeutic range of the drug.

17 So a lot of pharmacological studies go into
18 it. You know, we do pharmacokinetics and
19 pharmacodynamics on these drugs. And if there is a
20 reason to give a loading dose, it is based on
21 pharmacodynamics -- or pharmacokinetics of the drug.

3 Q. And if nothing like that has been
4 established, would you give a patient a medication
5 with a loading dose?

6 A. No.

8 A. In fact, I have some patients who come to me
9 and they say, "Well, you know, sometimes my blood
10 pressure is high so I take two of my pills." I
11 discourage them.

12 I say, "That's not how medications work. We
13 have a therapeutic range. You've gotta take your
14 medications on a regular basis."

15 Q. So it's safe to say that, if the only active
16 agent in the clinical protocol isn't described with
17 a loading dose, you wouldn't, on your own, tell a
18 patient to use a larger amount as a loading dose to
19 kick things off?

20 MR. WILKERSON: Objection. Form.

21 A. I can't think of an example of any
22 medications where I've done that. I don't see any



Ground 3 – “Without Pre-Loading”

2 Q. And if you were participating in a clinical
3 study as a treating physician, would you add a
4 loading dose of the active agent if the clinical
5 study did not explicitly call for a loading dose?

6 A. So if I was one of the investigators on a
7 clinical study, no, I would follow the protocol for
8 the clinical study.

9 Q. And what would the FDA do if you deviated
10 from the protocol for the clinical study?

11 A. I don't know what the FDA would do, but the
12 clinical protocol has to be followed. And the
13 clinical protocol usually is reviewed by the FDA
14 before a Phase 3 clinical study is done.

15 Q. And would the patient's data be included in
16 the study or need to be removed, if you added a
17 loading dose on your own outside of the boundaries
18 of the protocol?

19 A. If the principal investigator thinks that
20 that's deviation from the protocol, I think they
21 would remove the patient.

Ground 3 – “Without Pre-Loading”

- '063 Patent (EX1001) and October 2020 provisional (EX1003) describe LoDoCo, COLCOT and LoDoCo2 as having a “daily use of low-dose (0.5mg) colchicine”:

RCTs that met the following criteria were included in the meta-analysis: 1) compared daily use of low-dose (0.5 mg) colchicine to placebo or no colchicine for secondary cardiovascular prevention; 2) the study reported at least one of

EX1001 at 19:4-13

EX1003 at 3:11-16

- No mention of a loading dose.
- **Conclusion:**
 - No loading dose in LoDoCo, COLCOT, LoDoCo2.
 - In line with Dr. Ridker and Dr. Ardehali testimony already cited.

➤ MHI told CADTH that LoDoCo did *not* having a loading dose

Table 7: Details of Included Studies in Patients With Coronary Artery Disease

Detail	LoDoCo2	LoDoCo
Designs and populations		
Study design	Double-blind RCT (pivotal)	RCT, open-label (observer-blinded)
Locations	Australia (13 centres), Netherlands (30 centres)	Australia (1 outpatient cardiology clinic)
Patient enrolment dates	Enrolment: August 2014 to December 2018 Trial end date: December 2019	Enrolment: August 2008 and May 2010 Trial end date: May 2012
Randomized (N)	5,522	532
Inclusion criteria	Adults aged 35 to 82 years with CAD on invasive angiography or CT angiography, or a coronary artery calcium score ≥ 400 Agatston units on a coronary artery calcium scan - Clinically stable for at least 6 months - Patients who had undergone CABG were eligible only if the CABG was performed more than 10 years ago, they had angiographic evidence of graft failure, or they had undergone percutaneous intervention since bypass surgery	Adults aged 35 to 85 years with angiographically proven CAD - Clinically stable for at least 6 months - No major competing comorbidities or contraindication to colchicine - Considered adherent to therapy and follow-up appointments - Patients who had undergone CABG eligible only if CABG was performed more than 10 years ago, they had angiographic evidence of graft failure, or they had undergone stenting since bypass surgery
Exclusion criteria	- Moderate to severe renal impairment (eGFR < 50 mL/min/1.73 m² or creatinine > 150 µmol/L) - Severe heart failure (NYHA class III or IV) - Moderate or severe valvular heart disease likely to require intervention - Peripheral neuritis, myositis, or marked myo-sensitivity to statins - Dependency, frailty, or estimated life-expectancy < 5 years - Requires long-term colchicine for another reason	NR
Drugs		
Intervention	Colchicine 0.5 mg once daily plus standard care	Colchicine 0.5 mg once daily plus standard care
Comparator(s)	Placebo plus standard care	Standard care

EX1053, Table 7

Table 6: Details of Included Studies in Patients With Acute Coronary Syndrome

Details	COLCOT	COPS
Designs and populations		
Study design	Double-blind RCT (pivotal)	Double-blind RCT
Locations	Canada, South America, Europe, Middle East, North Africa (total 167 sites)	Australia (17 hospitals)
Patient enrolment dates	December 2015 to August 2018 Database lock: August 2019	December 2015 and September 2018 Database lock: NR
Randomized (N)	4,745	795
Inclusion criteria	Adults who experienced MI in past 30 days - Had completed planned coronary revascularization procedure - Were treated according to national guidelines (antiplatelet, statin, RAAS inhibitor, and beta-blocker, where indicated)	Patients 18 to 85 years of age who presented to hospital with ACS (symptoms of acute myocardial ischemia with elevated troponin or ECG changes) - Had CAD (≥ 30% luminal stenosis in any epicardial vessel of ≥ 2.5 mm diameter) on angiography - Were managed with PCI or medical therapy
Exclusion criteria	- Poorly controlled medical condition (e.g., NYHA class III or IV HF, LVEF < 35%, stroke within past 3 months, or other major condition) - Type 2 index MI (secondary to ischemic imbalance) - Prior CABG within past 3 years - Current cardiogenic shock or hemodynamic instability - Cancer or lymphoproliferative disease in past 3 years - Inflammatory bowel disease or chronic diarrhea - Pre-existing progressive neuromuscular disease or sustained CPK level > 3 times ULN (unless due to MI) in past 30 days - Recent laboratory abnormalities (e.g., creatinine > 2 times ULN, ALT > 3 times ULN, total bilirubin > 2 times ULN) - Cirrhosis, chronic active hepatitis, or severe hepatic disease - History of drug or alcohol misuse - Current colchicine or chronic systemic corticosteroid use	- CAD requiring surgical revascularization - Pre-existing long-term use of colchicine or immunosuppressants - Pre-existing use of strong CYP3A4 or P-glycoprotein inhibitors - Severe renal insufficiency (eGFR < 30 mL/min/1.73 m²) - Severe hepatic insufficiency - Known active malignancy
Drugs		
Intervention	Colchicine 0.5 mg once daily plus standard care	Colchicine 0.5 mg twice daily for 1 month, then 0.5 mg once daily for 11 months in addition to standard care

EX1053, Table 6

Ground 3 – “Without Pre-Loading”

- MHI described LoDoCo as not having a loading dose before EMA

In recent years, low-dose colchicine has been evaluated for its effect on CV events in patients with CAD. Results of the LoDoCo (Low-Dose Colchicine) [5.4 Nidorf *et al.*, 2013] trial suggested that long term low-dose administration of colchicine (0.5 mg/day) may significantly decrease the risk of CV complications in patients with stable coronary disease. This finding was confirmed with the recently published results of the large scale, randomized, placebo controlled pivotal LoDoCo2 trial in 5522 patients with chronic coronary disease [5.4 Nidorf *et al.*, 2020].

In contrast to the LoDoCo, and LoDoCo 2 supportive studies which were conducted in stable CAD patients, **the COPS study is another supportive study** conducted with low dose colchicine in patient with ACS. This trial is relevant for the MAA since it included patients with ACS and colchicine treatment for at least 12 months, but the dose is not the one proposed for the MA (1 mg/day for month 1 and 0.5 mg after).

EX1074



Ground 3 – Following PCI

- LoDoCo (EX1007) taught “wherein percutaneous coronary intervention [PCI] was performed for treating the patient’s MI” (claim 1)

(12) United States Patent Nidorf	(10) Patent No.: (45) Date of Patent:	US 10,206,891 B2 *Feb. 19, 2019
(54) METHOD OF TREATING CARDIOVASCULAR EVENTS USING COLCHICINE CONCURRENTLY WITH AN ANTIPLATELET AGENT	2008/0039408 A1 2/2008 Freudenberg 2009/0093548 A1 4/2009 Davis et al. 2009/0170952 A1 7/2009 Davis 2009/0229155 A1 12/2009 Yang 2009/0313430 A1 12/2009 Sun et al. 2011/0046227 A1 2/2011 Davis 2011/0046228 A1 2/2011 Davis 2011/0190397 A1 8/2011 Davis 2015/0094322 A1 4/2015 Riel 2015/0094323 A1 4/2015 Riel	
(71) Applicant: Murray and Poole Enterprises Limited, Gibraltar (GB)		
(72) Inventor: Mark Nidorf, Menora (AU)		
(73) Assignee: MURRAY AND POOLE ENTERPRISES LTD, Gibraltar (GB)		
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal dis- claimer.		
(21) Appl. No.: 15/663,148		
(22) Filed: Jul. 28, 2017		
(65) Prior Publication Data US 2017/0326083 A1 Nov. 16, 2017		
Related U.S. Application Data		
(63) Continuation of application No. 14/603,049, filed on Jan. 22, 2015, now Pat. No. 9,744,144, which is a continuation-in-part of application No. PCT/AU2013/001261, filed on Nov. 1, 2013.		
(30) Foreign Application Priority Data Nov. 2, 2012 (AU) 2012/904828 Nov. 5, 2012 (AU) 2012/904868		
(51) Int. Cl. A61K 31/65 (2006.01) A61K 45/06 (2006.01) A61K 31/616 (2006.01) A61K 31/57 (2006.01) A61K 31/365 (2006.01)		
(52) U.S. Cl. CPC A61K 31/65 (2013.01); A61K 31/37 (2013.01); A61K 31/365 (2013.01); A61K 31/616 (2013.01); A61K 45/06 (2013.01)		
(58) Field of Classification Search None See application file for complete search history.		
(56) References Cited U.S. PATENT DOCUMENTS 3,173,876 A 3/1965 Zubrin 3,276,586 A 10/1966 Rosen 3,541,005 A 11/1970 Strathmann et al. 3,541,006 A 11/1970 Biedler et al. 3,546,142 A 12/1970 Michalski et al. 4,285,987 A 8/1981 Ayer et al. 8,415,395 B1 4/2013 Davis et al. 2002/0017335 A1 2/2002 Hedden 2006/0171948 A1 8/2006 Weissstein et al. 2006/0286108 A1 12/2006 Bell		
	FOREIGN PATENT DOCUMENTS CN 1939290 A 4/2007 CN 101485637 A 7/2009 CN 101485638 A 7/2009 CN 101526990 A 9/2009 CN 101732274 A 6/2010 JP 2000034224 A 2/2000 JP 205523885 A 8/2005 JP 2011140498 A 7/2011 JP 2012519725 A 8/2012 JP 2012736846 A 12/2012 JP 201310873 A 8/2013 WO 1992015282 A2 9/1992 WO 2003051329 A 7/2003 WO 2007048804 A2 4/2007 WO 2008131192 A2 10/2008 WO 2010046628 A1 4/2010 WO 2010103365 A 9/2010 WO 2011060256 A 5/2011 WO 2012100949 A1 8/2012 WO 2012100949 A 9/2012 WO 2013155478 A1 10/2013 WO 2014066944 A1 5/2014	
	OTHER PUBLICATIONS Adler et al., “Colchicine treatment for recurrent pericarditis: a decade of experience,” <i>Circulation</i> , 97:2183-2185, 1998. Antonopoulos et al., “Statins as Anti-inflammatory agents in Atherosclerosis: Molecular mechanisms and lessons from the recent clinical trials,” <i>Curr. Pharma. Design</i> , 18:1519-1530, 2012. Critchenden, D., et al., “Colchicine Use Is Associated with decreased prevalence of Myocardial Infarction in Patients with Gout,” <i>J.</i> <i>Rheumatol.</i> , 39:1458-1464, 2012. Finisheva et al., “Colchicine for the prevention of Postpericarditis Syndrome,” <i>Herz</i> , 27(8):791-794, 2002. Gabrielian, R.S., et al., “Comparative effects of losartan and losartan colchicines combination therapy in unstable angina patients with hyperuricaemia,” <i>Eur J. Echocardi.</i> , 7:583, 2006. (Continued)	
	ABSTRACT Methods of treating and/or preventing a cardiovascular event in a patient, the method comprising orally adminis- tering a colchicine to a patient who is receiving concurrent treatment with at least one antiplatelet agent, thereby treat- ing and/or preventing the cardiovascular event in the patient are provided.	
	31 Claims, No Drawings	

ary outcomes were analysed similarly. In addition, the primary analysis was stratified by gender, age, diagnosis of diabetes, past myocardial infarction, unstable angina, coronary bypass surgery, coronary angioplasty, and therapy with aspirin, clopidogrel or both, high dose statin therapy (de-
fined as a dose of statin equivalent to atorvastatin of 40 mg or more), beta blockers, calcium blockers and ACE inhibi-
tors.

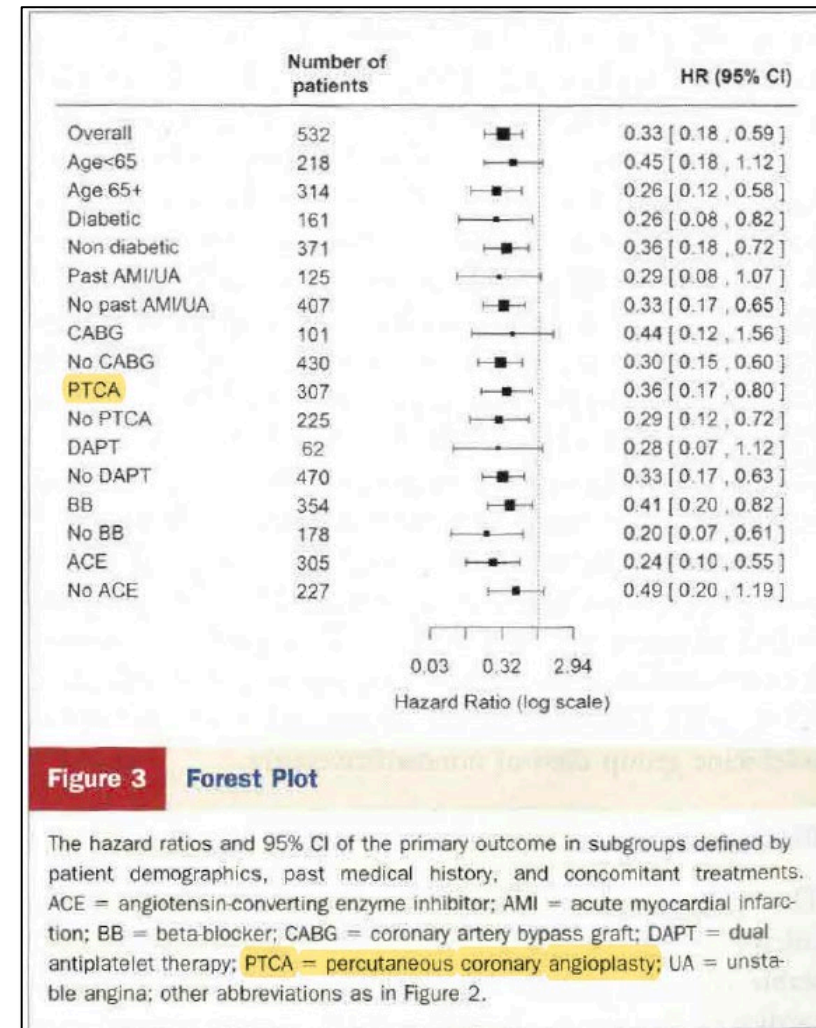
Ground 3 – Following PCI

- LoDoCo publication (EX1020) also taught “following PCI”

	Control	Treatment
Total	250	282
Mean age, yrs	67 ± 9.2	66 ± 9.6
Male	222 (89)	251 (89)
Diabetes	69 (28)	92 (33)
Smoker	14 (6)	10 (4)
Past AMI or UA	61 (24)	64 (23)
CABG	39 (16)	62 (22)
PTCA	138 (55)	169 (60)
Aspirin and/or clopidogrel	235 (94)	262 (93)
DAPT	24 (10)	38 (13)
High-dose statin	235 (94)	271 (96)
Beta-blocker*	178 (71)	176 (62)
Calcium channel blocker†	25 (10)	52 (18)
ACE inhibitor	150 (60)	155 (55)

Values are n, mean ± SD, or n (%). *p < 0.05. †p < 0.01 for the comparison of the distribution between treatment and control.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; DAPT = dual antiplatelet therapy (aspirin and clopidogrel); PTCA = percutaneous coronary angioplasty; UA = unstable angina.





Ground 3 – Motivation to Reduce TTI

- There was motivation to reduce TTI to “within about 3 days of MI”
 - Trend towards reducing TTI in stable patients
 - Routine optimization
 - 0-3, 4-7, >8 days is part of the “the usual journey of patients with MI”
 - ESC Guidelines
 - To maximize the treatment benefits
 - Before hospital discharge to improve patient compliance
- There was a reasonable expectation of success to reduce TTI to “within about 3 days of MI”
- Dr. Ridker discussed how a POSA would view all this information to reach “within about 3 days.”
- MHI has not produced any further evidence to suggest otherwise.

Ground 3 – Motivation to Reduce TTI

- LoDoCo and COLCOT were both directed to “stable” patients.
 - Those who can be discharged from the hospital, typically 2-3 days post-MI.
- Dr. Ridker discusses this in his first declaration. EX1049 ¶¶ 37-42, 146.

41. COLCOT also taught treating stabilized post-MI patients, as reflected in its eligibility criteria requiring that “[p]atient *must have completed any planned percutaneous revascularization procedures* associated with his or her qualifying myocardial infarction.”⁴⁰ COLCOT Protocol further taught initiating treatment within 30 days post-MI but only “*after having completed any planned percutaneous revascularization procedures* associated with their initial infarction.”⁴¹ As I explained above, this means that acute MI has been stabilized after percutaneous revascularization cleared the underlying arterial thrombosis and restored cardiac blood flow. Reinforcing that the patients are stable, COLCOT Protocol eligibility criteria excluded patients “with a poorly controlled medical condition,” such as certain types of heart attack, “recent stroke (within the past 3 months),” and patients “currently in cardiogenic shock or with hemodynamic instability” are excluded from the study.⁴²

EX1049 at ¶ 41

Ground 3 – Motivation to Reduce TTI

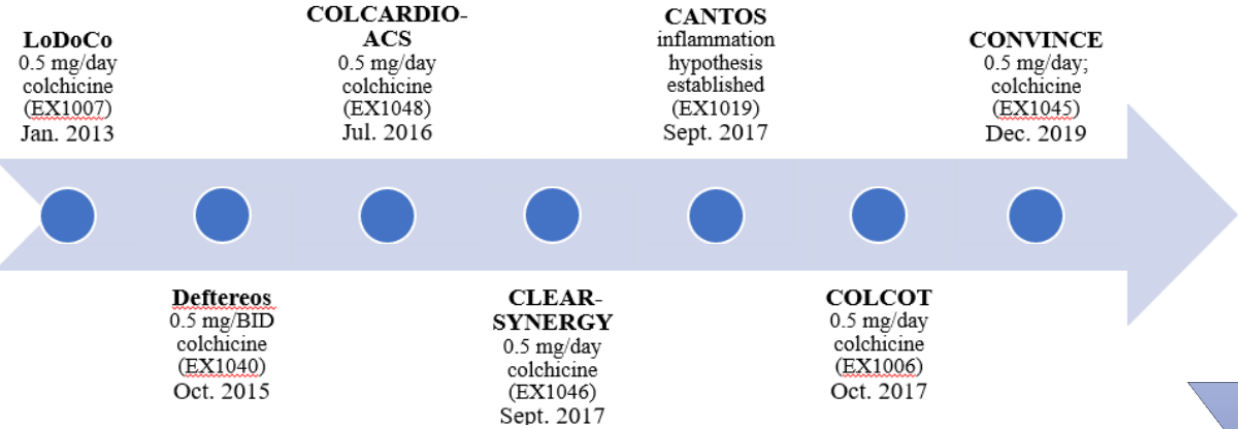
- MHI incorrectly argues that COLCOT “included patients that were stable.” Paper 37 at 20.

40. Petitioner incorrectly asserts that Nidorf and the COLCOT Protocol teach administering a low dose of colchicine without a loading dose.³⁹ However, rather than teaching that deviation from the previous standard, those studies were silent regarding use of a loading dose.⁴⁰ Thus, a POSA would not assume one way or the other regarding the use of a loading dose from these references, and this claim limitation is not taught in the prior art. In any event, as discussed above, the patients in both Nidorf and the COLCOT Protocol involved patients that were stable, and a POSA would not have made any determinations about excluding a loading dose based on patients that are stable.

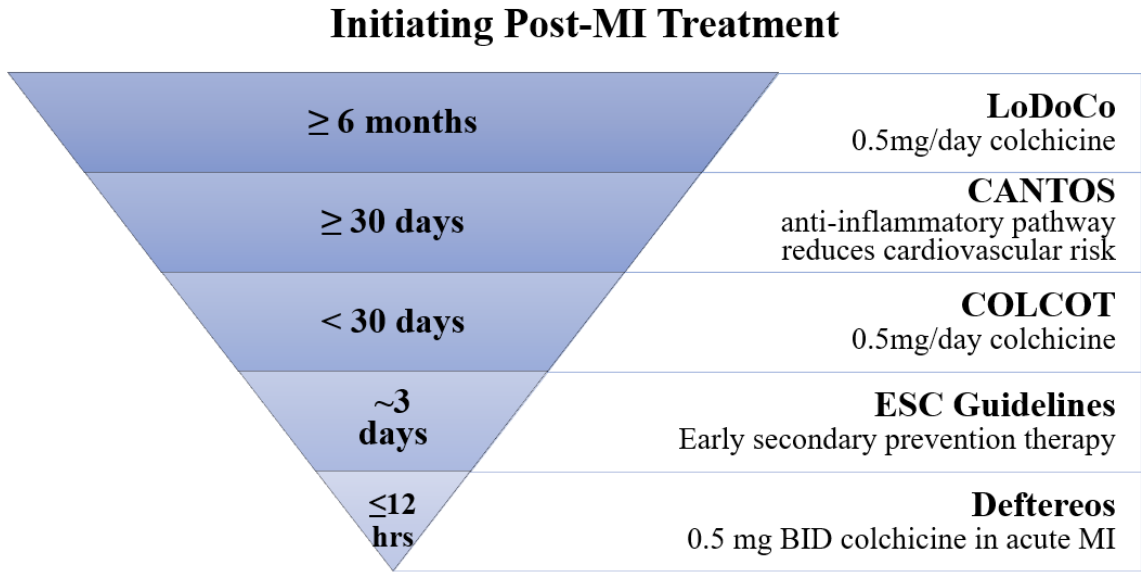
EX2001



Ground 3 – Motivation to Reduce TTI



LoDoCo (EX1007): at least 6 months post event
Deftereos (EX1040): within 12 hours post-MI to be safe
COLCARDIO-CAS (EX1048). 4-6 weeks post ACS event
CLEAR-SYNERGY (EX1046): within 72 hours of the index PCI
CANTOS: (EX1019): at least 30 days post-MI
COLCOT (EX1006): within 30 days post-MI
Hennessy (EX1028): acute MI within the prior 7 days



Ground 3 – Motivation to Reduce TTI

- There was a reasonable expectation of success of starting colchicine treatment within 3 days of an MI.
 - Low-dose colchicine was known in the art to work for stable patients.
 - There was no reason in the art to fear that low-dose colchicine – known for decades if not centuries to be a safe anti-inflammatory – would magically not work if started early after stabilization.
 - Dr. Ridker:
 - *“In my opinion, however, following the success of LoDoCo, initiating 0.5 mg/day colchicine within 30 days post-MI as disclosed in COLCOT Protocol, including at around day 3 post-MI, would have been consistent with quality care for other chronic therapies used on a long-term basis to reduce atherosclerotic risk which skilled cardiologists routinely start upon MI patient stabilization and prior to hospital discharge, and would have been obvious, especially in view of COLCOT Protocol and ESC Guidelines.... Essentially, after the success of CANTOS with initiating anti-inflammatory treatment as soon as 30 days post-MI, it would have been obvious to the skilled cardiologist to reduce the colchicine post-MI initiation time period to within the COLCOT 30-day window including to around 3 days post-MI as used with other secondary preventive therapy.”* EX1049 ¶¶ 145.



Ground 3 – Motivation to Reduce TTI

- There was motivation to reduce TTI through routine optimization.
 - “Initiation times within this prior art range are presumptively obvious and not overcome here by any unexpected results or evidence of criticality.” *E.I. DuPont de Nemours & Co. v. Sunvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“presumption of obviousness” for values within prior art range).” Pet. 38-39.
 - This is supported by “ESC Guidelines teaches initiating secondary preventative therapy at or prior to post-MI hospitalization discharge, corresponding to around day 2 or 3 post-MI.” Pet. 39 (citing Ex. 1009 at 24, 30, 33; Ex. 1049 ¶ 159).
 - Institution Decision got this right and nothing has changed.

Ground 3 – Motivation to Reduce TTI

- Additional motivation to start secondary prevention therapy sooner than later:
 - Provide potential better outcomes
 - Known better patience compliance

tion. Lipid-lowering treatment should be started as early as possible, as this increases patient adherence after discharge, and given as high-intensity treatment, as this is associated with early and sustained clinical benefits.⁴ The intensity of statin therapy should be

EX1009

7.1.6 Adherence to treatment

Low treatment adherence is an important barrier to achieving optimal treatment targets and is associated with worse outcomes.³¹⁷

EX1009

Early Statin Treatment Following Acute Myocardial Infarction and 1-Year Survival

Ulf Stenestrand, MD

Lars Wallentin, MD, PhD

for the Swedish Register of Cardiac Intensive Care (RIKS-HIA)

THE SCANDINAVIAN SIMVASTATIN Survival Study,¹ the Cholesterol And Recurrent Events trial,² and the Long-term Intervention with Pravastatin in Ischaemic Disease trials³ have demonstrated that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) initiated 3 to 6 months after acute myocardial infarction (AMI) reduces mortality in patients with elevated cholesterol levels. Among high-risk individuals with high cholesterol levels but without previous manifestations of coronary artery disease, statin treatment as primary prevention reduces the risk of subsequent coronary events.^{4,5} Even though there are indications that early statin treatment initiated during the hospital stay for acute coronary syndromes would be beneficial,⁶⁻⁹ the only clinical trial that has studied early statin intervention in acute coronary syndromes is the recently completed but not yet published Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study.¹⁰ Thus, the proportion of patients with AMI who are treated with statins while in the hospital varies among hospitals. Therefore, we investigated the relationship between 1-year mortality and statin treatment initiated before or at the time of hospital discharge in a large cohort of unselected patients with AMI admitted to the coronary care units of Swedish hospitals during 1995-1998.

Context Randomized trials have established statin treatment as secondary prevention in coronary artery disease, but it is unclear whether early treatment with statins following acute myocardial infarction (AMI) influences survival.

Objective To evaluate the association between statin treatment initiated before or at the time of hospital discharge and 1-year mortality after AMI.

Design and Setting Prospective cohort study using data from the Swedish Register of Cardiac Intensive Care on patients admitted to the coronary care units of 58 Swedish hospitals in 1995-1998. One-year mortality data were obtained from the Swedish National Cause of Death Register.

Patients Patients with first registry-recorded AMI who were younger than 80 years and who were discharged alive from the hospital, including 5528 who received statins at or before discharge and 14071 who did not.

Main Outcome Measure Relative risk of 1-year mortality according to statin treatment.

Results At 1 year, unadjusted mortality was 9.3% (1307 deaths) in the no-statin group and 4.0% (219 deaths) in the statin treatment group. In regression analysis adjusting for confounding factors and propensity score for statin use, early statin treatment was associated with a reduction in 1-year mortality (relative risk, 0.75; 95% confidence interval, 0.63-0.89; $P=.001$) in hospital survivors of AMI. This reduction in mortality was similar among all subgroups based on age, sex, baseline characteristics, previous disease manifestations, and medications.

Conclusions Early initiation of statin treatment in patients with AMI is associated with reduced 1-year mortality. These results emphasize the importance of implementing the results of randomized statin trials in unselected AMI patients.

JAMA. 2001;285:430-436

www.jama.com

METHODS

The Swedish Register of Cardiac Intensive Care, also known as the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA), registers all patients admitted to the coronary care units of participating hospitals. Information is reported on case record forms that include 100 variables. On admission, 30 variables are recorded, including information on age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, previous angina pectoris, previous MI, previous coronary revascularization, previous medications, symptoms, and electrocardiogram changes at entry and specified

time points (previous refers to events occurring or medication started before the current admission) (TABLE 1). During the hospital stay, another 37 variables are recorded regarding biochemical markers, echocardiography, reperfusion treatment, pharmacological treatment, interventional procedures, major arrhythmias, and other major complications. At discharge, 33 vari-

Author Affiliations: Department of Cardiology, University Hospital of Linköping, Linköping, Sweden (Dr Stenestrand); Department of Cardiology, University Hospital of Uppsala, Uppsala, Sweden (Dr Wallentin). **Participating Centers in the Swedish Register of Cardiac Intensive Care** are listed at the end of this article. **Corresponding Author and Reprints:** Ulf Stenestrand, MD, Department of Cardiology, University Hospital of Linköping, SE 58185 Linköping, Sweden (e-mail: stenestrand@riks-hia.se).

430 JAMA, January 24/31, 2001—Vol 285, No. 4

EX1008

Ground 3 – Motivation to Reduce TTI

- Motivation to start secondary prevention therapy earlier due to “the usual journey of patients with MI.” EX1005 at 4094 (citing, e.g., EX1011), 4098; EX1078 at 68:13-22.

Cut-offs for time-to-treatment initiation of colchicine

Three different cut-offs for TTI were used in order to determine the association between early initiation of therapy and clinical outcomes. These cut-offs were determined based on the usual journey of patients with MI.^{10,11} The first 30-day post-MI timeline was divided into three independent periods of time and analysed as such: from Day 0 to 3, referring to in-hospital management; from Day 4 to 7, referring to early post-discharge period, and from Day 8 to 30, referring to late post-discharge period.

EX1005 at 4094



Ground 3 – Motivation to Reduce TTI

- Dr. Ardehali and Dr. Ridker both agree that secondary therapies such as colchicine should be initiated prior to hospital discharge.

So what I will probably do if this drug gets approved by the FDA is I'm gonna tell my residents, as soon as they are -- you know, the patient goes to the cath lab and they come back, I would say this patient should be on statins, they should be on beta blockers, their blood pressure should be controlled, their diabetes should be controlled, their -- you know, cholesterol should be controlled, they should also be on colchicine while they are in the hospital. So that's how this is gonna change our practice.

Ardehali EX1076

11 A Oh, it's a good idea to do so.
12 Q And as you said, the patient is
13 generally, in the modern environment, released
14 from the hospital at two, two and a half, three
15 days. Right?
16 A Yes. And -- and perhaps I should
17 explain why it's a good idea to do so. I mean --
18 I mean, you know, when a -- when a patient goes
19 home from what has really been a life-changing
20 event in his or her life, we as cardiologists want
21 them on the long-term therapies that we have proof
22 work over the long haul to prevent them from

Ridker EX2071

1 having a second heart attack or second stroke or a
2 catastrophic death.
3 And we've learned from just a bit of
4 common sense, I suspect, and people that actually
5 study this sort of thing that initiating these
6 therapies that are standard secondary prevention
7 therapies. If I fail to do that at discharge when
8 the patient is stable, as you say, sometime at day
9 two is pretty typical, they might not see their
10 primary care physician for three or four months,
11 they may not see their community cardiologist for
12 quite a while, and I'd hate to have the patient
13 have to wait until then to get a therapy that
14 might save their life. That would be not great
15 care.

EX1082



Ground 3 – Motivation to Reduce TTI

- ESC Guidelines (EX1009) would have been relevant to the question of when to initiate treatment of stable MI patients because:
 - ESC Guidelines taught when to treat **stable MI patients**, a concept directly related to the challenged claims.
 - ESC Guidelines were a widely recognized definition of the best-practice standard-of-care treatment of ST-elevation MI patients, a population encompassed by the COLCOT study, shortly, *i.e.*, within the **same time period** (1-3 days, after MI).
 - Statins were common first-line treatments for stable MI, and concepts driving timing of treatment of stable MI patients would have been highly relevant regardless of the active agent.

Ground 3 – Motivation to Reduce TTI

- MHI incorrectly argues that improving patient compliance requires hindsight.

2. Improving patient compliance for motivation requires hindsight.

Petitioner also alleges a POSA would have been motivated to initiate colchicine treatment in post-MI patients before the patient leaves the hospital, for example, within 3 days. Reply at 17. However, such a motivation would only occur *after* a POSA determines that initiating colchicine so early was not harmful and effective, something not done before the '063 patent. Thus, although EX1009 discloses initiating certain drugs shortly after an MI in order to improve patient compliance, none of those drugs are colchicine.

Paper 37 at 21

- New sur-reply argument that was never previously raised.
- Incorrect because at least Deftereos (EX1040) already showed initiating low dose colchicine treatment within 12 hours post-MI to be safe.



Ground 3 – Motivation to Reduce TTI

- There was no hindsight, teaching away, or unpredictability as MHI alleges.
- MHI provided a list of publications mostly *sans pin-point citations* to support its otherwise unsubstantiated assertions.

Many common, but severe, CV events were (and remain) well-understood to be attributable to multiple factors, and thus effectiveness of new therapies for preventing CV events is highly unpredictable. *Id.* For example, a POSA would have known that different studies investigated models for predicting recurrent CV disease with varying results. See, e.g., compare EX2073 with EX2074.

A POSA would have also understood that even if the risk of recurrent CV events was known to increase, “[p]redictors and prognosis of a recurrent MI with contemporary management are not well known.” EX2058; see also EX2059 (teaching that risk window for post-MI stroke was longer than thought, but still not well-understood).

While it was known that inflammation can play a role in the treatment of CV events and the prevention of recurrent events, and colchicine was understood to act as an anti-inflammatory before 2019, the scope of inflammation’s role and colchicine’s effectiveness to treat and prevent CV events was highly unpredictable.

The nine most relevant publications regarding studies of colchicine’s effectiveness in treating and preventing CV events demonstrate the high degree of unpredictability in targeting protein inhibition for inflammatory pathway disruption to treat or prevent CV events and disease. See EX2009; EX2054; EX2064; EX1020; EX2065; EX2055; EX1028; EX1022; and EX2056.

O’Keefe, Raju, Hennessy, Akodad, and Tong found that low-dose colchicine was **not effective** to treat certain CV events when compared to placebo. Conversely, Deftereos 2013, Nidorf 2013, Nidorf 2020, and Tardif 2019 showed that low-dose colchicine could be effective at treating certain CV events when compared to placebo.

The failure of O’Keefe, Raju, Hennessy, Akodad, and Tong demonstrate the high unpredictability of the field, the lack of any reasonable expectation of success, and supports objective indicia of nonobviousness.

Later studies including Shah failed to show reduction in PCI-related MI or major cardiovascular events (see EX2066 at 1) providing further evidence of the continued unpredictability in the field.

Ground 3 – Motivation to Reduce TTI

- MHI ignores Dr. Ridker’s second declaration where Dr. Ridker explained that MHI’s publications were inappropriate.
- MHI chose not to depose Dr. Ridker or question his testimony on this topic.

Table 1	
Category	Publications
Clinical endpoints, unstable patients with acute coronary syndrome, intermediate sample size	EX2056
Clinical endpoints, patients with stable atherosclerotic disease, intermediate or large sample size	EX1020 EX1022 EX2065
Surrogate endpoints, unstable patients with acute coronary syndrome or acute stroke, small sample size	EX1028 EX2054 EX2055 EX2066
Surrogate endpoints, stable patients with atherosclerotic disease or undergoing angioplasty, small sample size	EX2063 EX2009 EX2064

EX1075



EX1020 = Nidorf 2013 “LoDoCo”
EX1022 = Tardif 2019 “COLCOT”
EX2065 = Nidorf 2020 “LoDoCo2”



EX1028, EX2054, EX2055, EX2066 relate to acute phase, unstable patients



Ground 3 – MHI's References Support Motivation

- EX1028, EX2054, EX2055, EX2066 investigate effect of colchicine on **acute** biomarkers and endpoints, not chronic atherosclerosis.
- MHI argues lack of effect in acute phase shows colchicine effect is unpredictable.
- But lack of effect in acute phase is not relevant to long term chronic atherosclerosis because different biologic processes operate:

reduction observed following recent myocardial infarction in COLCOT. Moreover, in contrast to the stable phase at day 2 and 3 following MI when patients are getting ready for hospital discharge to home, even today it has not been shown that colchicine is clinically effective in the immediate hours following acute MI, an unstable and dangerous time period when a different set of biologic processes related to coronary reperfusion and restoration of oxygen flow are dominant. Thus, while it

Ridker 1st Decl. EX1049 ¶ 7

17. Studies such as EX1028, EX2054, EX2055, EX2056, and EX2066 were conducted in the setting of acute ischemia or acute coronary syndromes, a setting where a very different biology is in play and where it remains uncertain as to whether colchicine is or is not effective. This is, however, irrelevant to the present discussion because COLCOT is a trial in stable patients. The studies in the acute setting are not informative about effectiveness in treating chronic atherosclerosis in stable patients.

Ridker 2nd Decl. EX1075 ¶ 17

Conclusion: No effect in acute phase → colchicine effect in COLCOT is on chronic atherosclerosis = LoDoCo.

- MHI's reliance on COPS (EX2056) is misguided.
 - COPS is completely different from COLCOT.
 - **Different** patients: Patients with **acute** coronary syndrome
 - **Different** dosage: **0.5 mg twice daily** for the first month, then 0.5 mg daily for 11 months
 - **Different** follow-up: Only 12 months
 - **Different** primary outcome: A composite of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke
 - Results: The addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months.
 - Conclusion: Not relevant or predictive of '063 Patent.

Circulation

ORIGINAL RESEARCH ARTICLE

Colchicine in Patients With Acute Coronary Syndrome

The Australian COPS Randomized Clinical Trial

Editorial, see p 1901

David C. Tong, PhD
: Jamie Layland, PhD

BACKGROUND: Inflammation plays a crucial role in clinical manifestations and complications of acute coronary syndromes (ACS). Colchicine, a commonly used treatment for gout, has recently emerged as a novel therapeutic option in cardiovascular medicine owing to its anti-inflammatory properties. We sought to determine the potential usefulness of colchicine treatment in patients with ACS.

METHODS: This was a multicenter, randomized, double-blind, placebo-controlled trial involving 17 hospitals in Australia that provide acute cardiac care service. Eligible participants were adults (18–85 years) who presented with ACS and had evidence of coronary artery disease on coronary angiography managed with either percutaneous coronary intervention or medical therapy. Patients were assigned to receive either colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months) or placebo, in addition to standard secondary prevention pharmacotherapy, and were followed up for a minimum of 12 months. The primary outcome was a composite of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke in a time to event analysis.

RESULTS: A total of 795 patients were recruited between December 2015 and September 2018 (mean age, 59.8±10.3 years; 21% female), with 396 assigned to the colchicine group and 399 to the placebo group. Over the 12-month follow-up, there were 24 events in the colchicine group compared with 38 events in the placebo group ($P=0.09$, log-rank). There was a higher rate of total death (8 versus 1; $P=0.017$, log-rank) and, in particular, noncardiovascular death in the colchicine group (5 versus 0; $P=0.024$, log-rank). The rates of reported adverse effects were not different (colchicine 23.0% versus placebo 24.3%), and they were predominantly gastrointestinal symptoms (colchicine, 23.0% versus placebo, 20.8%).

CONCLUSIONS: The addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in patients with ACS and was associated with a higher rate of mortality.

REGISTRATION: URL: <https://www.anzctr.org.au>; Unique identifier: ACTRN12615000861550.

The full author list is available on page 1899.

Key Words: acute coronary syndrome
■ colchicine ■ coronary artery disease
■ inflammation

Sources of Funding, see page 1899

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<https://www.ahajournals.org/journal/circ>

1890 November 17, 2020

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MHI EXHIBIT 2056



Ground 3 – Ridker on COPS

- Dr. Ridker confirmed COPS (EX2056) is irrelevant in his deposition.

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1 Q Okay. And although there is some
2 differences in the studies, I don't disagree with
3 that. You would agree that they both investigated
4 different outcomes for using half a milligram --
5 strike that. Strike that. We can restart.

6 Both studies, COPS and COLCOT,
7 investigated using low-dose colchicine after
8 myocardial infarction. Right?

9 A Oh, no. Come on. Matt, please.

10 Q No.

11 A These are extremely different contexts,
12 right? One is -- one is acute coronary ischemia
13 and one is stable atherosclerosis. We're not
14 going back there, are we?

15 Q I -- I -- I will caveat, I will grant
16 you, and we will totally agree that there are
17 differences in the studies, right?

18 A (Indiscernible.)

19 Q That's fine. We're not disagreeing.

20 A I'm just simply saying because I don't
21 want to chase dogs' tails that much longer.

22 Q Okay.

230

1 way. So if you really want to go through this, we
2 could pull the supplement.

3 Q Well, I guess from this paragraph, my
4 question is, could there be patients included that
5 were stable?

6 A The description here is patients who are
7 in the acute phase that we talked about earlier,
8 very early on. But if you want to go to the -- I
9 mean, this is -- this is a very brief summary of a
10 protocol. If you want to go to some other
11 material, we can go through the protocol.

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6 The authors here are describing patients
7 in that acute setting who have just within the
8 last -- I can't tell. There's no timing here
9 listed. But you get the sense it's within minutes
10 to hours of when they have had their angio- --
11 percutaneous intervention, if they got it. But
12 then it also says for medical therapy at the
13 discretion of the treating team, so there's a lot
14 of differences here.

15 But the authors are -- what is this one
16 here? I mean, the -- the -- again, I'm going off
17 the other one because -- or you can scroll up.
18 Maybe -- maybe scroll up here. Go back to the
19 abstract.

20 The -- the authors usually say in their
21 background what it is they intend to study. And
22 so they say here, We sought to determine potential

1 usefulness in colchicine treatment with patients
2 with acute coronary syndrome.

3 So they're looking at that very early
4 period that we were talking about before, which --
5 which is quite different than what COLCOT did.
6 That's -- that's the point here, right?

EX1082



Objective Indicia

- The '063 Patent cannot be saved by objective indicia.
- There were **no credible results**, expected, unexpected, or otherwise.
- EX1005 (“Bouabdallaoui”) presents a ***post hoc subgroup analysis*** that lacks statistical power to draw the conclusions it draws and the '063 Patent claims (that 0-3 days TTI is unexpectedly beneficial).
- EX1005’s assertions of alleged superiority of 0-3 days TTI are ***biologically implausible***.
- The same is true for 4-7 days TTI.
- MHI has never disputed these points or this detailed explanation by Dr. Ridker.



Objective Indicia

- MHI never challenged or rebutted **any** of M&P's statistics arguments.
 - MHI **never** asked Dr. Ridker about his statistics analysis.
 - MHI **never** countered Drs. Fiolet and Cornel's (EX1012 or EX1080 at 3-5) assessment questioning the findings of Bouabdallaoui (EX1005).
 - MHI **never** provided their own expert opinion about statistics.
 - Dr. Ardehali did not provide any statistics arguments. In fact, he admitted his only knowledge about statistics comes from one undergraduate class.
 - In contrast, Dr. Ridker has a sophisticated level of biostatistics understanding.



Objective Indicia

- MHI's only argument against the statistics is that "[t]he mere fact that the data shows a benefit across 30-days and within 3 days does not show that it defies 'biological plausibility.' Rather, it merely shows the data were insufficient to draw conclusions for specific days between 8-30." Sur-reply at 25.
- This is an admission that the COLCOT data were insufficient to draw conclusions for 0-3 days!
 - There were more patients in 8-30 day time-period than in 0-3 day time-period (2,748 vs. 1,193).
 - The 0-3 day subgroup is only 26% of the total COLCOT cohort.
 - COLCOT patients were stable. Thus, very few patients were actually in days 0-1.
 - No mention of 4-7 day subgroup.
- This proves that the TTI analysis was never properly powered to look at any smaller time periods (subgroups) or to make any conclusions about specific time periods.



Objective Indicia

Application No. 17/097,285
Response dated April 13, 2021
Reply to Office Action of January 13, 2021

Docket No.: 50761-029001

Rejection under 35 U.S.C. § 103

Claims 13, 15-17, and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Hennessy.

The Office states (pages 4 and 5):

With respect to claim 13, inventor distinguishes over the prior art in that a patient with atherosclerotic coronary artery disease is [not] explicitly taught. However, as is well-known in the art, most myocardial infarctions are due to atherosclerotic coronary artery disease.

* * *

With respect to claims 15-17 and 20 inventor principally distinguishes over the prior art in that a particular delivery vehicle for the colchicine is taught. However, the cited reference is a general teaching and one of ordinary skill – **absent unexpected results** – would have found it obvious, before the effective filing date of the instant invention, to administer the appropriate dosage (i.e. 0.5 mg) of colchicine by any appropriate means, such as a tablet, a coated tablet or a film-coated tablet, motivated by ordinary clinical observations.

Claims 13, 15-17, and 20 depend from claim 1. As explained below, the features of claim 1 are nonobvious over Hennessy.

The method of claim 1 is based on the **inventor's finding that administration of colchicine within about 3 days of an MI leads to patient outcomes that are significantly better when compared to a placebo**. This statistically significant effect is not seen when colchicine is administered between 4 and 7 days after an MI. In particular, as is shown in Table 3 of the specification (reproduced below for reference with highlighting added), **administration of colchicine within about 3 days of an MI yields a statistically significant reduction in the composite of primary endpoints** (cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization) in comparison to a placebo, whereas administration of colchicine between days 4 to 7 and on or after day 8 do not. Here, 4.3% of patients receiving colchicine within 3 days of an MI reached a primary endpoint, whereas 8.3% receiving a placebo within 3 days of an MI reached a primary endpoint. **These results show a statistically significant benefit for a patient receiving colchicine within about 3 days of an MI**. Patients receiving colchicine within about 4 to 7 days of an MI do not show a statistically significant benefit. Applicant submits that this result is nonobvious over the teachings by Hennessy where patients received colchicine within 7 days of an MI.

Applicant respectfully submits that the obviousness rejection of claims 13, 15-17, and 20 should be withdrawn.



Objective Indicia

- EX1005 data is misinterpreted *post hoc* analysis which was the result of ***brainstorming*** sessions.
- EX1005 is a *post hoc* subgroup analysis of COLCOT which was never designed to test TTI.
 - COLCOT did not provide sufficient statistical power to test the 0-3 day TTI subgroup.
 - COLCOT only provided statistical power to test within 30 days.

Objective Indicia

➤ Subgroup analyses are unreliable.

Commentary

Debate: Subgroup analyses in clinical trials – fun to look at, but don't believe them!

Peter Sleight

John Radcliffe Hospital, Oxford, UK

Abstract

Analysis of subgroup results in a clinical trial is surprisingly unreliable, even in a large trial. This is the result of a combination of reduced statistical power, increased variance and the play of chance. Reliance on such analyses is likely to be more erroneous, and hence harmful, than application of the overall proportional (or relative) result in the whole trial to the estimate of absolute risk in that subgroup. Plausible explanations can usually be found for effects that are, in reality, simply due to the play of chance. When clinicians believe such subgroup analyses, there is a real danger of harm to the individual patient.

Keywords: astrology, clinical trials, overview, play of chance, randomization

Astrology in the International Study of Infarct Survival trials

In retrospect, perhaps one of the most important results in the ISIS trials was the analysis of the results by astrological star sign. All of the patients had their date of birth entered as an important 'identifier'. We were therefore able to divide our population into 12 subgroups by astrological star sign. Even in a highly positive trial such as ISIS-2 [3], in which the overall statistical benefit for aspirin over placebo was extreme ($P < 0.00001$), division into only 12 subgroups threw up two (Gemini and Libra) for which aspirin had a nonsignificantly adverse effect ($9\% \pm 13\%$)

➤ Tardif concurred with this view, admitting PHAs are “less strict,” “less stringent,” and “less strong,” and admitting “prespecified” is “better.”

Objective Indicia

ARTICLES

Subgroup analysis and other (mis)uses of baseline data in clinical trials

Susan F Assmann, Stuart J Pocock, Laura E Enos, Linda E Kasten

Summary

Background Baseline data collected on each patient at randomisation in controlled clinical trials can be used to describe the population of patients, to assess comparability of treatment groups, to achieve balanced randomisation, to adjust treatment comparisons for prognostic factors, and to undertake subgroup analyses. We assessed the extent and quality of such practices in major clinical trial reports.

Methods A sample of 50 consecutive clinical-trial reports was obtained from four major medical journals during July to September, 1997. We tabulated the detailed information on uses of baseline data by use of a standard form.

Findings Most trials presented baseline comparability in a table. These tables were often unduly large, and about half the trials inappropriately used significance tests for baseline comparison. Methods of randomisation, including possible stratification, were often poorly described. There was little consistency over whether to use covariate adjustment and the criteria for selecting baseline factors for which to adjust were often unclear. Most trials emphasised the simple unadjusted results and covariate adjustment usually made negligible difference. Two-thirds of the reports presented subgroup findings, but mostly without appropriate statistical tests for interaction. Many reports put too much emphasis on subgroup analyses that commonly lacked statistical power.

Interpretation Clinical trials need a predefined statistical analysis plan for uses of baseline data, especially covariate-adjusted analyses and subgroup analyses. Investigators and journals need to adopt improved standards of statistical reporting, and exercise caution when drawing conclusions from subgroup findings.

Lancet 2000; **355**: 1064-69

New England Research Institutes, Watertown, MA, USA (S F Assmann PhD, L E Enos MD, L E Kasten MA); and Medical Statistics Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (Prof S J Pocock PhD)
Correspondence to: Prof Stuart J Pocock

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THE LANCET • Vol 355 • March 25, 2000

Introduction

For most randomised clinical trials, substantial baseline data are collected on each patient at randomisation. These data relate to demographics, medical history, current signs and symptoms, and quantitative disease measures (including some measured again later in the study as outcomes). Gathering of such baseline data seems to have four main aims. First, baseline data are used to characterise the patients included in the trial, and to show that the treatment groups are well balanced. Second, randomisation may include some means of balancing or stratification on a few key factors. Third, for analysis of outcome by treatment group, covariate adjustment may be used to take account of certain baseline factors. Fourth, subgroup analyses may be carried out to assess whether treatment differences in outcome (or lack thereof) depend on certain characteristics of patients.

Statistical reporting of clinical trials has improved, many journals have statistical refereeing, and clearer guidelines to authors' may further improve reporting quality. However, insufficient attention is paid to the quality and extent of reporting on these uses of baseline data.

We aimed to describe and critically evaluate current practice on the use of baseline data in clinical-trial reports in major medical journals, and to make recommendations to enhance the quality of future reporting, especially on the dangers of overemphasising subgroup analyses.

Methods

We handsearched all reports of clinical trials with individual randomisation of patients during July to September, 1997, in *BMJ*, *JAMA*, *The Lancet*, and *New England Journal of Medicine*. Crossover trials and cluster-randomised trials were excluded, as were small trials with less than 50 patients per group. Any trials with non-random allocation would also have been excluded, but none were identified. We decided that a sample size of 50 trials was large enough to provide representative and reliable results, and was small enough to allow thorough assessment.

Thus 50 trial reports were obtained: 24 in *New England Journal of Medicine*, 15 in *The Lancet*, six in *JAMA*, and five in *BMJ* (see *Lancet* website for references: www.thelancet.com). A standard form detailing the uses of baseline data was piloted on a few trials to achieve consistency of data extraction. Discrepancies were resolved by discussion and agreement, usually when the report was not clear. The data extracted for each report are outlined in the panel.

Results

The 50 randomised trials surveyed had the following characteristics: 39 trials had two randomised treatments, five had three treatments, and six (two with a factorial design) had four treatments. The number of patients

The use of significance tests for detecting baseline differences is questionable.⁷ Any differences are either due to chance or to flawed randomisation (a serious bias uncorrectable by statistical analysis). Our 6% rate of

Thus, such data exploration is not bad on its own provided investigators (and readers) do not overemphasise subgroup findings. Also, the underuse of statistical tests of interaction means the play of chance gets inadequate recognition. Reliance on subgroup p values is misleading. If the overall result is significant, almost inevitably some subgroups will and some will not show significant differences depending on chance and

As in this case, interaction tests commonly lack statistical power (ie, the trial is not large enough to detect subgroup findings). Hence one is inevitably left in doubt as to whether a suggestive subgroup analysis (eg, with interaction $p=0.05$ to $p=0.15$) is simply due to chance or merits further investigation. Even after reporting a non-significant interaction test, investigators may still overinterpret subgroup findings.

Statistical tests of interaction (that assess whether a treatment effect differs between subgroups) should be used rather than inspection of subgroup p values, which often encourages inappropriate subgroup claims. Only if the statistical interaction test supports a subgroup effect should the conclusions be influenced. Even then, the emphasis should depend on biological plausibility, the number of subgroup analyses, their prespecification, and the statistical strength of evidence, recognising that most subgroup claims are prone to exaggerate the truth.

Objective Indicia

➤ EX1005 did not provide a breakdown of baseline characteristics for the placebo and colchicine arms in each subgroup, meaning **selection bias in the 0-3 day subgroup cannot be ruled out.**

- Drs. Fiolet and Cornel noted:
 - *“An important caveat in the interpretation of this finding is that **not all unequally distributed characteristics** were used in adjustment of these estimators.”*
EX1012, 4.

- Dr. Ridker agrees. EX1049 ¶ 235.

Characteristics	TTI 0-3 days N = 1193	TTI 4-7 days N = 720	TTI ≥ 8 days N = 2748	p*	p**
Age (years)- mean ± SD	59.1 ± 10.8	60.1 ± 11.0	61.3 ± 10.4	<0.0001	<0.0001
Male sex- no. (%)	980 (82.2%)	605 (84.0%)	2189 (80.0%)	0.014	0.071
BMI (kg/m ²)- mean ± SD	28.1 ± 4.6	27.7 ± 4.6	28.6 ± 4.8	<0.0001	0.004
Current Smoking- no. (%)	522 (43.8%)	306 (42.6%)	554 (20.2%)	<0.0001	<0.0001
History of Hypertension-no. (%)	490 (41.1%)	343 (47.6%)	1544 (56.2%)	<0.0001	<0.0001
History of Diabetes no. (%)	208 (17.4%)	130 (18.1%)	604 (22.0%)	0.001	0.001
Prior MI-no. (%)	170 (14.3%)	111 (15.4%)	470 (17.1%)	0.070	—
Prior PCI no. (%)	182 (15.3%)	107 (14.9%)	494 (18.0%)	0.035	0.037
Prior CABG-no. (%)	34 (2.9%)	30 (4.2%)	82 (3.0%)	0.218	—
Prior HF-no. (%)	14 (1.2%)	12 (1.7%)	64 (2.3%)	0.046	0.017
Prior Stroke or TIA-no. (%)	20 (1.7%)	21 (2.9%)	78 (2.8%)	0.084	—
PCI associated with the index event-no. (%)	1143 (95.8%)	685 (95.1%)	2508 (91.3%)	<0.0001	<0.0001
Medication use-no. (%)					

Objective Indicia

- EX1005 did not conduct **statistical tests of interaction** which are necessary to determine whether a treatment effect differs **between the subgroups**.
- Drs. Fiolet and Cornel noted:
 - “The authors of [Bouabdallaoui] did not report whether the differences in observed effect size between strata were statistically significant.” EX1012, 3-4.
 - Dr. Ridker added:
 - “...the primary composite endpoint for patients with TTI 0-3 days has a hazard ratio range that overlaps with those of the patients with TTI 4-7 days and 8-30 days.... [t]his type of data are insufficient to support a conclusion that initiating colchicine treatment within 3 days in the COLCOT study achieved superiority over other treatment initiation periods.” EX1049 ¶ 241.

Table 3 Efficacy endpoints according to time-to-treatment initiation (N = 4661, colchicine vs. placebo)

Endpoints	TTI 0–3 days, N = 1193	TTI 4–7 days, N = 720	TTI ≥ 8 days, N = 2748
	Colchicine vs. placebo, no. (%) HR (95% CI); P	Colchicine vs. placebo, no. (%) HR (95% CI); P	Colchicine vs. placebo, no. (%) HR (95% CI); P
Primary composite endpoint	26 (4.3%) vs. 49 (8.3%) 0.52 (0.32–0.84); P = 0.007	22 (6.0%) vs. 21 (5.9%) 0.96 (0.53–1.75); P = 0.896	77 (5.7%) vs. 99 (7.1%) 0.82 (0.61–1.11); P = 0.200
CV death	2 (0.3%) vs. 2 (0.3%) 1.04 (0.15–7.37); P = 0.970	2 (0.5%) vs. 4 (1.1%) 0.45 (0.08–2.46); P = 0.356	15 (1.1%) vs. 18 (1.3%) 0.89 (0.45–1.76); P = 0.734
Resuscitated cardiac arrest	1 (0.2%) vs. 3 (0.5%) 0.33 (0.03–3.20); P = 0.340	2 (0.5%) vs. 1 (0.3%) 1.90 (0.17–20.95); P = 0.600	2 (0.1%) vs. 2 (0.1%) 1.02 (0.14–7.22); P = 0.986
MI	17 (2.8%) vs. 29 (4.9%) 0.58 (0.32–1.05); P = 0.071	16 (4.4%) vs. 9 (2.5%) 1.67 (0.74–3.78); P = 0.218	52 (3.8%) vs. 59 (4.2%) 0.93 (0.64–1.35); P = 0.710
Stroke	1 (0.2%) vs. 5 (0.8%) 0.21 (0.02–1.81); P = 0.156	1 (0.3%) vs. 3 (0.8%) 0.28 (0.03–2.71); P = 0.272	2 (0.1%) vs. 11 (0.8%) 0.19 (0.04–0.84); P = 0.029
Urgent hospitalization for angina requiring coronary revascularization	6 (1.0%) vs. 17 (2.9%) 0.35 (0.14–0.88); P = 0.026	4 (1.1%) vs. 6 (1.7%) 0.63 (0.18–2.24); P = 0.476	15 (1.1%) vs. 26 (1.9%) 0.61 (0.32–1.16); P = 0.131
Secondary composite endpoint	20 (3.3%) vs. 36 (6.1%) 0.55 (0.32–0.95); P = 0.031	18 (4.9%) vs. 16 (4.5%) 1.04 (0.53–2.03); P = 0.919	67 (4.9%) vs. 77 (5.5%) 0.92 (0.66–1.28); P = 0.629
All-cause death	6 (1.0%) vs. 6 (1.0%) 1.03 (0.33–3.19); P = 0.962	8 (2.2%) vs. 7 (2.0%) 1.03 (0.37–2.84); P = 0.957	26 (1.9%) vs. 31 (2.2%) 0.90 (0.53–1.51); P = 0.684
All coronary revascularizations	33 (5.5%) vs. 51 (8.7%) 0.63 (0.40–0.97); P = 0.037	25 (6.9%) vs. 18 (5.1%) 1.41 (0.76–2.61); P = 0.275	72 (5.3%) vs. 94 (6.7%) 0.81 (0.59–1.10); P = 0.172

The primary composite endpoint included CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The secondary composite endpoint included CV death, resuscitated cardiac arrest, MI, and stroke. Only the initial event was counted in the analyses of time to first event for the primary composite endpoint and for the secondary composite endpoint.

Covariates included in the stepwise multivariable Cox regression models are: age; sex; BMI; smoking status; history of diabetes; history of hypertension; history of dyslipidaemia; prior MI; prior coronary revascularization (prior PCI or prior CABG); prior heart failure. All models also included TTI, group and the interaction between group and TTI. CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; HR, hazard ratio; PCI, percutaneous coronary intervention; TTI, time-to-treatment initiation.

Objective Indicia

- EX1005 *did* provide statistical tests of interaction when discussing baseline characteristics in Table 2.

Table 2 Baseline characteristics according to time-to-treatment initiation

Characteristics	TTI 0–3 days (N = 1193)	TTI 4–7 days (N = 720)	TTT ≥ 8 days (N = 2748)	<i>p</i> ^a	<i>p</i> ^b
Age (years), mean ± SD	59.1 ± 10.8	60.1 ± 11.0	61.3 ± 10.4	<0.0001	<0.0001
Male sex, no. (%)	980 (82.2)	605 (84.0)	2189 (80.0)	0.014	0.071
BMI (kg/m ²), mean ± SD	28.1 ± 4.6	27.7 ± 4.6	28.6 ± 4.8	<0.0001	0.004
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History of hypertension, no. (%)	490 (41.1)	343 (47.6)	1544 (56.2)	<0.0001	<0.0001
History of diabetes, no. (%)	208 (17.4)	130 (18.1)	604 (22.0)	0.001	0.001
Prior MI, no. (%)	170 (14.3)	111 (15.4)	470 (17.1)	0.070	—
Prior PCI, no. (%)	182 (15.3)	107 (14.9)	494 (18.0)	0.035	0.037
Prior CABG, no. (%)	34 (2.9)	30 (4.2)	82 (3.0)	0.218	—
Prior HF, no. (%)	14 (1.2)	12 (1.7)	64 (2.3)	0.046	0.017
Prior stroke or TIA, no. (%)	20 (1.7)	21 (2.9)	78 (2.8)	0.084	—
PCI associated with the index event, no. (%)	1143 (95.8)	685 (95.1)	2508 (91.3)	<0.0001	<0.0001
Medication use, no. (%)					
Aspirin	1181 (99.0)	715 (99.3)	2709 (98.6)	0.219	—
Other anti-platelet agent	1177 (98.7)	708 (98.3)	2682 (97.6)	0.072	—
Statin	1188 (99.6)	708 (98.3)	2719 (98.9)	0.024	0.047
Beta-blocker	1093 (91.6)	642 (89.2)	2408 (87.6)	0.001	0.0003
Time from index MI to randomization (days), mean ± SD	2.1 ± 0.8	5.1 ± 1.1	20.8 ± 6.6	—	
Time from index MI to PCI (days), mean ± SD	0.4 ± 0.7	1.4 ± 1.8	1.8 ± 3.6	<0.0001	<0.0001
Time from PCI to randomization (days), mean ± SD	1.6 ± 0.9	3.7 ± 1.9	18.8 ± 7.3	<0.0001	<0.001

Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 431 patients (213 in the colchicine group and 218 in the placebo group) and body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively). Date of birth was not a required field because it was considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by 1 July. CABG, coronary artery bypass graft surgery; HF, heart failure; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

^aGroup comparison TTI 0–3 vs. TTI 4–7 vs. TTI ≥ 8 days.

^bGroup comparison TTI 0–3 vs. TTI ≥ 8 days.

Objective Indicia

➤ Figure 2 undermines conclusions of EX1005

– Drs. Fiolet and Cornel concluded:

- “whether this parabolic relation of treatment initiation and effect size—with greater effect size seen in both very early (<3 days) and very late (>21 days) treatment initiation—reflects separate biologic mechanisms of the drug *or is a play of chance* cannot be distinguished from these data.” Pet. 71; EX1012, 4.

– Dr. Ridker agreed saying:

- “Thus, like myself, Drs. Fiolet and Cornel also agree that in the absence of a plausible biological mechanism, a skilled cardiologist would *interpret this parabolic data as reflecting an artifact of the post hoc analysis rather than an actual treatment effect.*” EX1049 ¶ 245.

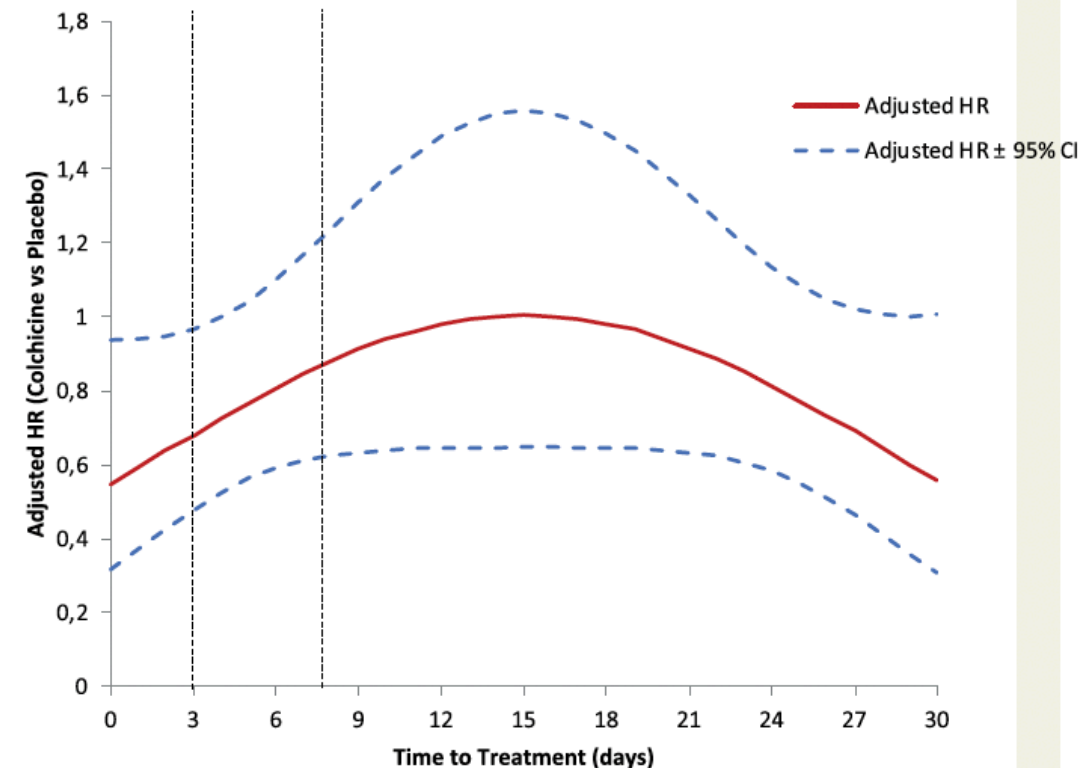


Figure 2 Associations between time-to-treatment initiation and the risk of occurrence of the primary composite endpoint. The adjusted hazard ratio and 95% confidence intervals come from a quadratic multivariable Cox regression model.

- There is **no biologically plausible explanation** for conclusions of EX1005.

- Dr. Ridker explained:

*“...the post-hoc subgroup analyses of Bouabdallaoui requires cardiovascular readers to accept the **improbable biologic notion that colchicine 0.5 mg treatment initiated at days 2 to 3 is “beneficial”** whereas the same treatment initiated between days 4 and 7 is “not beneficial”, yet then becomes “beneficial again” when started after 8 days, even though in all cases the drug was to be continued as therapy over a period of several years, and the vast majority of clinical events avoided in comparison to those allocated to placebo occurred well after the 30-day initiation period had ended.” EX1049 ¶ 227.*

ARTICLES

Subgroup analysis and other (mis)uses of baseline data in clinical trials

Susan F Assmann, Stuart J Pocock, Laura E Enos, Linda E Kasten

Subgroup analysis

Investigators should be cautious when undertaking subgroup analyses. Subgroup findings should be exploratory, and only exceptionally should they affect the trial's conclusions. Editors and referees need to correct any inappropriate, overenthusiastic uses of subgroup analyses.

The credibility of subgroup analyses is improved if confined to the primary outcome and to a few predefined subgroups, on the basis of biologically plausible hypotheses. This might include factors used to stratify randomisation. Investigators should recognise whether their trial is not large enough to detect realistic subgroup effects, and be particularly wary of claiming a treatment difference in a subgroup when the overall treatment comparison is not significant. Such subgroup rescues of otherwise negative trials are often unwarranted, unless the evidence is statistically convincing and clinically sensible.

Statistical tests of interaction (that assess whether a treatment effect differs between subgroups) should be used rather than inspection of subgroup p values, which often encourages inappropriate subgroup claims. Only if the statistical interaction test supports a subgroup effect should the conclusions be influenced. Even then, the emphasis should depend on biological plausibility, the number of subgroup analyses, their prespecification, and the statistical strength of evidence, recognising that most subgroup claims are prone to exaggerate the truth.

In multicentre trials, centre-adjusted analysis and treatment-by-centre interactions may be useful secondary analyses, but should not replace the overall results.

Objective Indicia

- **Pre-specified** subgroup analyses are “better” according to Tardif but still unreliable.
- Prespecified subgroup analysis of COLCOT shows that colchicine was effective in:
 - in men but not women;
 - in patients with no prior MI/stroke but not with prior MI/stroke; and
 - in patients without PCI/CABG but not with PCI/CABG.
 - Contradicts findings of LoDoCo and COLCOT.

Table S3. Primary Efficacy Composite Endpoint in Prespecified Subgroups†.

Subgroup	Colchicine	Placebo	Hazard ratio (95% CI)
<i>no. of patients with event/total no. of patients (%)</i>			
All patients	131/2366 (5.5%)	170/2379 (7.1%)	0.77 (0.61-0.96)
Smoking			
Non-smoker	47/787 (6.0%)	52/797 (6.5%)	0.90 (0.61; 1.34)
Previous smoker	46/871 (5.3%)	77/872 (8.8%)	0.59 (0.41; 0.85)
Active smoker	38/708 (5.4%)	41/708 (5.8%)	0.93 (0.60; 1.44)
History of diabetes			
Yes	40/462 (8.7%)	65/497 (13.1%)	0.65 (0.44; 0.96)
No	91/1904 (4.8%)	105/1882 (5.6%)	0.85 (0.64; 1.13)
History of hypertension			
Yes	83/1185 (7.0%)	112/1236 (9.1%)	0.76 (0.57; 1.01)
No	48/1181 (4.1%)	58/1143 (5.1%)	0.80 (0.54; 1.17)
Prior MI			
Yes	46/370 (12.4%)	47/397 (11.8%)	1.05 (0.70; 1.58)
No	85/1996 (4.3%)	123/1982 (6.2%)	0.68 (0.51; 0.89)
Prior PCI or CABG			
Yes	48/419 (11.5%)	57/447 (12.8%)	0.91 (0.62; 1.34)
No	83/1947 (4.3%)	113/1932 (5.8%)	0.72 (0.54; 0.95)
Prior stroke or TIA			
Yes	8/55 (14.5%)	9/67 (13.4%)	1.09 (0.42; 2.82)
No	123/2311 (5.3%)	161/2312 (7.0%)	0.76 (0.60; 0.96)
Sex‡			
Male	94/1894 (5.0%)	135/1942 (7.0%)	0.70 (0.54; 0.91)
Female	37/472 (7.8%)	35/437 (8.0%)	0.99 (0.63; 1.58)
White blood cell count¶			
Below median	41/660 (6.2%)	46/637 (7.2%)	0.85 (0.56; 1.29)
Above median	34/637 (5.3%)	44/664 (6.6%)	0.80 (0.51; 1.25)



Grounds 1 and 4

Ground	Claims	Basis	References
1	1-13, 17-26, 28, 40-46, 49, 50	§ 102	Bouabdallaoui
2	27, 29-36, 39	§ 102	COLCOT Protocol
3	1-50	§ 103	Nidorf in view of COLCOT Protocol, ESC Guidelines, and COLCRYS
4	1-26, 28, 40-50	§ 103	Bouabdallaoui in view of COLCRYS

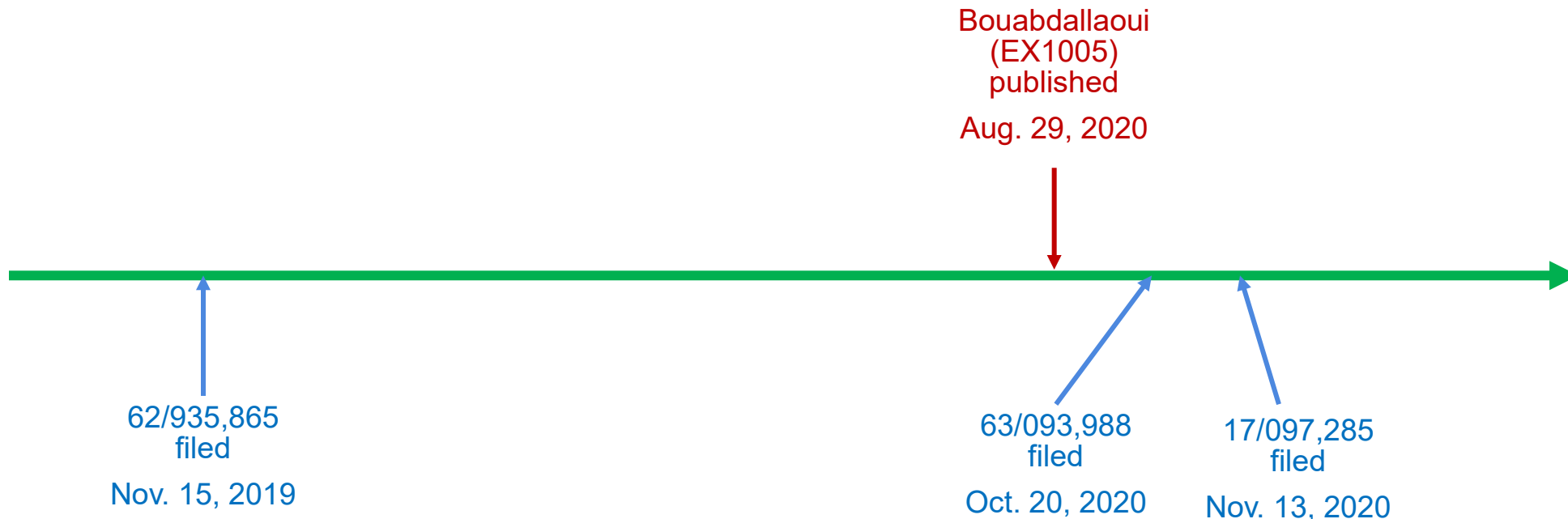
Grounds 1 and 4

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

8. A method of treating a patient alter having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

Grounds 1 and 4 - Priority

- Claims 1-26, 28 and 40-50 are **not** entitled to the first provisional filing date.
- **No** support in first provisional for 0-3 days TTI or 4-7 days TTI.
- As a result, Bouabdallaoui is prior art to those claims because it is “by another.”
- Institution Decision got this right and nothing has changed since then.



Grounds 1 and 4 - Burdens

- Is EX1005 §102(a)(1) prior art “by another”?
- Burden-shifting framework applies. See *Dynamic Drinkware*.
- Petitioner has met its initial burden of production.
 - EX1005 on its face satisfies burden of production.
 - Board agreed, instituting trial on this ground saying the issue “will benefit from development during trial.” Inst. Dec’n at 56.
- Burden of production has since been with and remains with MHI.
 - MHI must have produced sufficiently corroborated evidence that 0-3 day TTI limitation was **solely** conceived by Tardif.
 - Corroboration is judged under the “rule of reason.” Paper 8 at 2.
 - MHI has not satisfied its burden of production.
 - Moreover, the evidence strongly suggests that Dr. Tardif was not the sole inventor.

Grounds 1 and 4 - Evidence

- Who conceived of the claimed subject matter with 0-3 days TTI?
 - EX1005 is “by another” unless MHI produces sufficient evidence that Dr. Tardif alone conceived of all claimed subject matter, including 0-3 days TTI.
 - Tardif is one of 24 authors.
 - Bouabdallaoui is first author, interpreted the statisticians’ findings, and wrote the manuscript.
 - MHI’s evidence
 - EX2011 (Tardif declaration)
 - EX2001 (Ardehali declaration)
 - EX2068 (Bouabdallaoui declaration)
 - Other evidence
 - EX1077 (Tardif cross examination)
 - EX1078 (Bouabdallaoui cross examination)

EX1005 at 1; Ardehali Decl. (EX2001) ¶¶ 30-31; Tardif Decl. (EX2011) ¶¶ 16-30; Bouabdallaoui Decl. (EX2068) ¶¶ 2-4, 8-10; Tardif Dep. Tr. (EX1077) at 69:6-11, 70:2-18, 70:20–71:3; Bouabdallaoui Dep. Tr. (EX1078) at 14:17–15:11, 16:6–17:8; 30:5-12; 36:2-15; 64:9–67:8; 71:10–75:22; 81:7–82:12; 86:2-6; 89:22–92:8; 105:5–108:6 .



Grounds 1, 4 – Tardif’s Waivering Evidence

2. I am the named inventor on U.S. patent No. 11,400,063 (“the ’063 patent”), which is the patent that it at issue in the Petition. (EX1001.) As stated in my affidavit to the United States Patent Office during prosecution of the ’063 patent, I am the sole inventor of the ’063 patent.

23. During prosecution of the ’285 application, I provided an affidavit stating that I am the inventor of the invention described in the application. (EX1002 at 338.) That statement was true at the time that I made it and remains true today. Also, during prosecution of the ’285 application, I instructed attorneys prosecuting the ’285 application to provide copies of the Tardif article and the Bouabdallaoui article to the patent Examiner. (EX1002 at 75-77.)

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention

EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

As the below named inventor, I hereby declare that:

This declaration ☐ The attached application, or
is directed to: ☒ United States application or PCT international application number 17/097,285
filed on 11/13/2020.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a

LEGAL NAME OF INVENTOR

Inventor: Jean-Claude TARDIF Date (Optional): 2021/01/15

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

Grounds 1, 4 – Tardif’s Irrelevant Evidence

16. To overcome the deficiencies of the LoDoCo study, I designed the COLCOT study. My goal with COLCOT was to conduct a large-scale,

17. I personally conceived of and designed the COLCOT study and its protocol. In preparing the protocol for the study, I received input from colleagues at MHI, but the study and its protocol were my conception and responsibility. I also obtained the funding to conduct the COLCOT study. (EX2016.)

18. In addition, I was the principal investigator for the COLCOT study.

outcomes were meaningful, I personally recruited investigators from 167 different facilities including MHI. These were investigators and clinics with which MHI

15; EX2014 at 6-7, 10-12; EX2015 at 6-8, 12-13.) Each site agreed that any results from the clinical study were confidential, were to be provided to MHI, and were intellectual property that was owned by MHI. (EX2012 at §§5, 7, 8; EX2013 at §§5, 7, 8; EX2014 at §§5, 7, 8; EX2015 at §§5, 7, 8.) Further, the investigators understood that MHI had the right of first publication, and that they were not permitted to publish any data without the prior approval of MHI. (EX2012 at §7; EX2013 at §§7,8; EX2014 at §7; EX2015 at §7.)

Grounds 1, 4 – Tardif’s Irrelevant Evidence

27. I am not the first named author of Bouabdallaoui, but that is immaterial. As seen from EX1005, I am listed on the first page of the article as the corresponding author. Those in the industry understand that the corresponding

28. I was the primary author of the Bouabdallaoui article. The article itself is based on a clinical study that I designed, developed, and served as the principal investigator on. The data generated from the clinical study that was included in Bouabdallaoui was collected, provided to me, and was analyzed at my direction. The co-authors on Bouabdallaoui were provided information about the COLCOT study results from me. As seen from the agreements with the investigators, MHI was provided data from the COLCOT study from all the individual study sites, and that data was the property of MHI. (EX2012 at §8;

29. I included the co-authors to acknowledge their assistance and work in obtaining and collecting the data for the COLCOT study. In fact, at the time Dr. Bouabdallaoui was relatively early in her career and I had her listed as the first author on the publication to acknowledge her assistance in conducting the trial as well as to provide a “first author” publication for her CV. However, as the basis of

Grounds 1 and 4 – Tardif's Evidence

30. In order to develop new ways to treat the serious conditions facing patients, clinicians need to be able to draw from the resources of the medical community without fear that their discoveries will lose intellectual property protection simply because they included those who provided resources as co-authors on an article describing their work. The Bouabdallaoui reference—a reference on which I am a co-author—is a publication of my invention or substantively the same subject matter of my invention by me with others who obtained the subject matter disclosed therein directly or indirectly from me.



Grounds 1 and 4 – Tardif’s Evidence

6 Q Do you believe you are the sole inventor
7 on this patent?
8 A Yes.

20 Q Did you come up with the idea to -- of the
21 zero- to three-, four- to seven-,
22 greater-than-eight-day time period?
1 CNSL S. PATEL: Asked and answered.
2 (OBJECTION)
3 THE WITNESS: Yes.

2 Q Did you check each claim of the patent
3 before deciding whether you are the sole inventor
4 of the patent?
5 CNSL S. PATEL: Objection to form.
6 (OBJECTION)
7 THE WITNESS: Well, that -- that was some
8 time ago, but I'm -- I don't remember by heart.
9 But I'm pretty sure we did.
10 CNSL J. BROUGHER:
11 Q Did you consult with a patent attorney
12 before you decided to name yourself as the only
13 inventor?
14 CNSL S. PATEL: Objection.
15 (OBJECTION)
16 THE WITNESS: The answer is yes. We -- we
17 work with a patent firm. I don't remember by
18 heart the discussions, no. But I'm sure we did.



Grounds 1, 4 – Ardehali's Unfounded Evidence

30. I understand from counsel that Bouabdallaoui is not prior art, because it is a publication authored by the inventor less than one year before the priority date by the inventor or by another who obtained the subject matter disclosed directly from the inventor. Counsel have asked me to evaluate whether a POSA would regard Dr. Tardif as the author of the Bouabdallaoui reference. It is my opinion that a POSA would regard Dr. Tardif as the author.

31. In medical publications, there are a variety of ways and conventions that the authors may be listed. In most medical publications, the first named author is not indicative of the lead author or investigator for the particular research reported. Rather, a lead author/investigator may choose to list the author alphabetically, or give a mentee the opportunity to be the first-named in recognition of their work. If, however, a POSA wanted to discover who was responsible for the article, its research, and protocols, she would look to the corresponding author. In the Bouabdallaoui article, the corresponding author is Dr. Tardif, who is also the sole inventor of the '063 patent. Therefore, it is my opinion that a POSA would regard Dr. Tardif as the author of Bouabdallaoui and the other named authors as contributors to the research. Therefore, the Bouabdallaoui article is either an article by the inventor, Dr. Tardif, or the subject matter of the article was obtained directly from him, and thus my understanding is the article is not prior art that anticipates the '063 patent.



Grounds 1 and 4 – Bouabdallaoui's Evidence

2. I am a co-author of Bouabdallaoui et al. "Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)," Eur. Heart J. (2020) 41, 4092–4099 ("Bouabdallaoui," EX1005). Bouabdallaoui et al. is a sub-analysis of the data obtained in a clinical investigation called the Colchicine Cardiovascular Outcomes Trial study, also known as the "COLCOT" study.

3. I did not develop the COLCOT study hypothesis and was not involved in conducting the main study. Along with the other listed co-authors, I worked on a secondary analysis of the study's results and participated in the writing of the article by Bouabdallaoui et al.

4. I do not consider myself an inventor of U.S. Patent No. 11,400,063 ("the '063 patent") (EX1001).

10. While I am the first named author of the Bouabdallaoui et al. article, Dr. Tardif is the corresponding author, which in academia indicates that the individual is the senior researcher responsible for the article. The corresponding author gets the article into publication and speaks on behalf of the other co-authors to the publishers and the readers. The corresponding author is responsible for, among other things, manuscript corrections, publishing agreements, and responding to inquiries about the article on behalf of the co-authors. Dr. Tardif asked me to be the first named author of the article because I was working under his guidance.

Grounds 1 and 4 – MHI’s Evidence

➤ What Does **Not** Matter

- Who “conceived and designed the COLCOT study and its protocol.”
- Who “recruited investigators.”
- Who “obtained the funding to conduct the COLCOT study.”
- Who “owns” the data generated by the study.
- Who has “first publication rights.”
- Who was the “corresponding author” of EX1005.
- Whether Dr. Bouabdallaoui “considers” herself to be an inventor.
- What Dr. Ardehali’s “opinion” of who the POSA would regard as the inventor.

➤ What **Does** Matter

- Whether Tardif’s claim of sole inventorship is **corroborated**.
- What actually happened regarding the conception of the 0-3 day TTI limitation?
- Who conceived of the 0-3 day TTI limitation?



Grounds 1 and 4 – Where is the Corroboration?

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Grounds 1 and 4 – What Actually Happened

- Dr. Bouabdallaoui revealed that TTI were products of group ***brainstorming sessions*** attended by her and others besides Tardif:
 - Dr. Tardif organized team brainstorming meetings to solicit from the attendees “any ideas that can ... come ... from the [COLCOT] database.”
 - Dr. Bouabdallaoui was there. So were others.
 - The idea to do a PHA of TTI came from these group brainstorming sessions.
 - We don’t know who had the 0-3 day TTI idea.
 - Only MHI knows and they have not revealed.
 - Nor do we know who first realized that the 0-3 day TTI subgroup had allegedly better results.
 - This is a clear failure to carry the burden to produce evidence in MHI’s exclusive possession.



Grounds 1 and 4 – What Actually Happened

- Why did Dr. Tardif not mention these team brainstorming meetings?
- Why didn't he offer – in light of these meetings – corroboration of his bald claim that the 0-3 days and 4-7 days and 8+ days TTIs were his ideas?
- Why did he not divulge any details whatsoever of his alleged conception?
- Why did MHI not offer any corroboration of his alleged conception?
 - No notes from these brainstorming meetings, no emails, no contemporaneous documents at all
 - No testimony from others at these brainstorming meetings (except Dr. Bouabdallaoui, whose testimony does not corroborate Dr. Tardif's)
 - No testimony from the patent attorney(s)



Grounds 1 and 4 – Brainstorming According to Bouabdallaoui

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3 THE WITNESS: As far as I remember, it's
4 not a one-person idea. This kind of discussions
5 are kind of outcomes of brainstorming that take
6 place. So as far as I remember, it's not a
7 person's idea. So these discussions or this
8 brainstorming outcomes are the results -- are
9 all -- have all been carried out under the
10 supervision of Dr. Tardif, who actually is the
11 main researcher of the study.

22 I'll try to explain the process. That's
1 to say, different members think about how to use
2 information that is included in COLCOT -- or
3 COLCOT. And it is in the framework of these kind
4 of meetings that decisions are made about the
5 analysis to be achieved. It's usually the main
6 researcher of the study, who in this case is
7 Dr. Tardif, who is the lead or who is the lead of
8 these discussions.



Grounds 1 and 4 – Brainstorming According to Bouabdallaoui

9 Q So whose idea was it to do the TTI post
10 hoc analysis that is reported in this paper that
11 is Exhibit 1005?

12 CNSL S. PATEL: Objection to form.
13 (OBJECTION)

14 THE WITNESS: So, as mentioned previously,
15 when the COLCOT study was published, we --
16 Dr. Tardif suggested to a number of the members of
17 his team to discuss any ideas that can be -- that
18 can come up from the -- from the database. So
19 there were brainstormings, discussions within the
20 team. These discussions were led by Dr. Tardif,
21 and the -- the team was -- I was part of the team.
22 I was working with him at that time.

2 Q Do you remember when these -- how many
3 brainstorming sessions took place regarding the
4 TTI analysis reported in this paper?

5 A I do not remember exactly.

6 Q Do you remember approximately when those
7 brainstorming sessions took place?

8 A It was after the main paper was published.
9 I'll say at the end of the 2019.

10 Q And do you remember who was presented at
11 those brainstorming discussions?

12 A It wasn't always the same people, but
13 Dr. Tardif's mentees at that time, the
14 statisticians, the other -- the other
15 investigators.

16 Q I'm sorry. Did you say "it was not always
17 the same group of people"?

18 A Yes, that was said.

19 Q Okay. And do you have a specific
20 recollection of a particular individual who said,
21 "Let's look at time to initiate treatment"?

22 A No, I do not.

7 Q So this paper looked at three different
8 TTI windows; correct?

9 A Mm-hmm, yes.

10 Q Okay. And one of them is from zero to
11 three days?

12 A Mm-hmm.

13 Q Another is from four to seven days, and
14 the last one is eight days or more?

15 A Yes.

16 Q Whose idea was it to look at those three
17 time intervals?

18 A I do not remember.



Grounds 1 and 4 – Brainstorming According to Bouabdallaoui

10 Q Okay. Can you just tell me how this post
11 hoc analysis was conducted. What happened?

12 A So, again, when you conduct a clinical
13 trial, you will come up with a database with a lot
14 of data, information. And then you always ask
15 yourself as a -- an investigator is there any
16 other -- other scientific questions that you may
17 be able to address using that database? So this
18 is when you bring all the team together and you
19 discuss what could be the questions that could be
20 answered. And this is how it happened.

21 Q Okay. All right. Those are the
22 brainstorming sessions you refer to?

1 A Yes.

18 Q Okay. And what was your role in this
19 process?

20 A So once the question -- once the results
21 are there, I worked on them. I interpreted them.
22 I gave interpretation. And I started working on
1 the manuscript. At each step, I was referring to
2 Dr. Tardif to have his feedback and to have his
3 opinion on what I was doing.

Grounds 1 and 4 – Evidence of Conception

ZERO EVIDENCE
CORROBORATING
DR. TARDIF AS SOLE
INVENTOR

CIRCUMSTANTIAL
EVIDENCE THAT
OTHERS AT LEAST
PARTIALLY
CONCEIVED OF
TTI LIMITATIONS

- The claimed TTIs arose during **brainstorming sessions** attended by many people, including Dr. B.
- Dr. B does **not** remember that the TTIs were Dr. Tardif's idea.
- Dr. B had experience doing time-based PHAs.
- Dr. B interpreted the statistical results.
- Dr. B wrote the manuscript for EX1005.
- Dr. B was not obligated to assign patent rights to MHI.
- Dr. B was excluded from the patenting process.
- Evidence linking Dr. B to the patent was removed.

Grounds 1 and 4 – Evidence Pointing to Dr. B.

- Dr. Bouabdallaoui is experienced in conducting time-based *post hoc* analyses.



HHS Public Access

Author manuscript

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Impact of Intubation Time on Survival following Coronary Artery Bypass Grafting: Insights from the Surgical Treatment for Ischemic Heart Failure (STICH) trial

Nadia Bouabdallaoui, MD¹, Susanna R. Stevens², Torsten Doenst, MD³, Krzysztof Wrobel, MD⁴, Denis Bouchard, MD, PhD¹, Marek A. Deja, MD⁵, Robert E. Michler, MD⁶, Yeow Leng Chua, MD⁷, Renato A. K. Kalil, MD, PhD⁸, Craig H. Selzman, MD⁹, Richard C. Daly, MD¹⁰, Benjamin Sun, MD¹¹, Ljubomir T. Djokovic, MD¹², George Sopko, MD¹³, Eric J. Velazquez, MD², Jean L. Rouleau, MD¹, Kerry L. Lee, Ph.D.², Hussein R. Al-Khalidi, Ph.D.², and STICH Trial Investigators



Grounds 1 and 4 – Evidence Pointing to Dr. B.

5	Q Okay. Are you an employee of MHI,
6	Montreal Heart Institute?
7	A Yes, I work at the MHI, and I am a
8	self-employed. I actually work as a self-employed
9	at the MHI, but I'm not an employee of the MHI.
10	And by the way, it's a point I'd like to underline
11	or highlight is that it's improper in my written
12	declaration or statement.

2	Q Dr. Nadia, do you know if you are legally
3	obligated to assign to MHI patent rights for
4	inventions that you create working for MHI?
5	CNSL S. PATEL: Same objection.
6	(OBJECTION)
7	THE WITNESS: No, I don't know.



Grounds 1 and 4 – Evidence Pointing to Dr. B.

2	Q Okay. So no one consulted with you before
3	a patent application was prepared?
4	CNSL S. PATEL: Asked and answered.
5	(OBJECTION)
6	THE WITNESS: No.

5	Q So did anyone inform you that your
6	initials were removed from the text of this
7	document before it became the 063 patent?
8	A No.

Grounds 1 and 4 – What Actually Happened

- MHI incorrectly argues that brainstorming sessions were directed to “other” *post-hoc* analyses.

³ Ignoring all the corroborating evidence, Petitioner alleges Dr. Bouabdallaoui’s testimony is the only credible account of the origination of the TTI subgroups. But Dr. Bouabdallaoui’s testimony unequivocally supports Dr. Tardif’s sole inventorship, and both witnesses were clear that additional brainstorming sessions addressed other post-hoc analyses that is not the subject matter of or claimed in the ’063 patent. EX1077 at 42:16-43:11; EX1078 at 14:17-15:11.

- *But see* EX1078 at 64:9-22, 65:2-22, 71:10–72:16, 81:7–82:12 (Dr. Bouabdallaoui testifying specifically about the brainstorming sessions that gave rise to the 0-3 day TTI limitation). Quoted in part on slides 77-79.
- Dr. Tardif **never** mentioned brainstorming sessions.

Grounds 1 and 4 – Dr. B’s Disavowal

- MHI argues Bouabdallaoui “disavowed” her inventorship.

conception. *Id.* Contrarily, here, Dr. Bouabdallaoui has disavowed her inventorship, not asserted it. Thus, in view of the declarations of Dr. Tardif and Dr. Bouabdallaoui, MHI has satisfied the requirements for confirming inventorship.

- But she is not qualified to make the legal determination of inventorship.
- She is qualified to tell us what happened; she (and only she) did, and those facts point to others besides Dr. Tardif having conceived (solely or jointly) of the claimed TTI limitations.
- The facts, not her wishes, control who is an inventor.

Grounds 1 and 4 – Improper New Argument

- MHI's surreply argument about correcting inventorship under 35 U.S.C. § 256 is belated.

C. Petitioner's Inventorship Position is Futile

Finally, even if the Board finds that the latest possible priority date should apply for claims 1, 8, and 28 and that Dr. Bouabdallaoui should be listed as an inventor, EX1005 is still not prior art. If it is held that Dr. Bouabdallaoui is an inventor, MHI can correct inventorship under 35 U.S.C. § 256. Even under Petitioner's reasoning, if Dr. Bouabdallaoui is an inventor, then EX1005 is the work of the inventor that was published less than one year before the latest possible priority date. Paper 7; Reply at 6.

- MHI has not sought permission to correct inventorship
- Such permission should not be given at this late stage.



Grounds 1 and 4 – MHI Hedges

- MHI **never** says that Tardif is **sole** inventor.
 - “Dr. Tardif’s declaration includes statements regarding the work he did to conceive, organize, and conduct the COLCOT trial, from which the results underwent a post-hoc analysis at his direction ...” Opp’n to Motion to Exclude at 9.
 - “Dr. Bouabdallaoui provided ... her opinion that she is not an inventor of the ’063 patent.” Opp’n to Motion to Exclude at 10.
 - “Rather than accept Dr. Bouabdallaoui’s disavowal of inventorship ...” Opp’n to Motion to Exclude at 10.
- MHI’s expert has a misunderstanding of inventorship.
- MHI hedges to say they can correct inventorship under 35 U.S.C. § 256 if required.



Motion to Exclude

- ¶¶ 16-59 of Ardehali First Declaration.
 - FRE 702 and 703
- ¶¶ 26-28 of Ardehali Suppl. Declaration
 - FRE 602
- ¶ 23 of Tardif Declaration
 - FRE 402 and 403
- ¶ 4 of Bouabdallaoui Declaration
 - FRE 402 and 403
- Exhibits 2002-10, 2012-16, 2054-66, 2069, 2070, 2073, and 2074
 - FRE 902, 401 and 402