CHAIRE BEAULIEU-SAUCIER EN PHARMACOGÉNOMIQUE DE L'UNIVERSITÉ DE MONTRÉAL

JUIN 2023

Simon de Denus, pharmacien, MSc (Pharm), PhD

Titulaire de la Chaire en pharmacogénomique Beaulieu-Saucier de l'Université de Montréal

Doyen, Professeur titulaire, Faculté de Pharmacie, Université de Montréal
Chercheur, pharmacien, Institut de cardiologie de Montréal

Directeur de la pharmacothérapie, Centre de Pharmacogénomique Beaulieu-Saucier de l'Université de Montréal

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

Faculté de pharmacie
Université de Montréal

Thèmes de recherche

Pharmacogénomique/
Génomique de
l'insuffisance cardiaque

Sexe et médicaments

Implantation de la
pharmacogénomique

Plan

- Résumé de la dernière année
- Activités en cours et à venir

Résumé de la dernière année – Principales publications/soumissions

- ALLO-MHI/LEVEL-PGx

Females present higher dose-adjusted drug concentrations of metoprolol and allopurinol/oxypurinol than males

Jessica Hindi[1,2,3] | Marc-Olivier Pilon[1,2,3] | Maxime Meloche[1,2,3] | Grégoire Leclair[1] | Essaïd Oussaïd[2,3] | Isabelle St-Jean[1] | Martin Jutras[1] | Marie-Josée Gaulin[2,3] | Ian Mongrain[2,3] | David Busseuil[2,3] | Jean Lucien Rouleau[2,4] | Jean-Claude Tardif[2,3,4] | Marie-Pierre Dubé[2,3,4] | Simon de Denus[1,2,3]

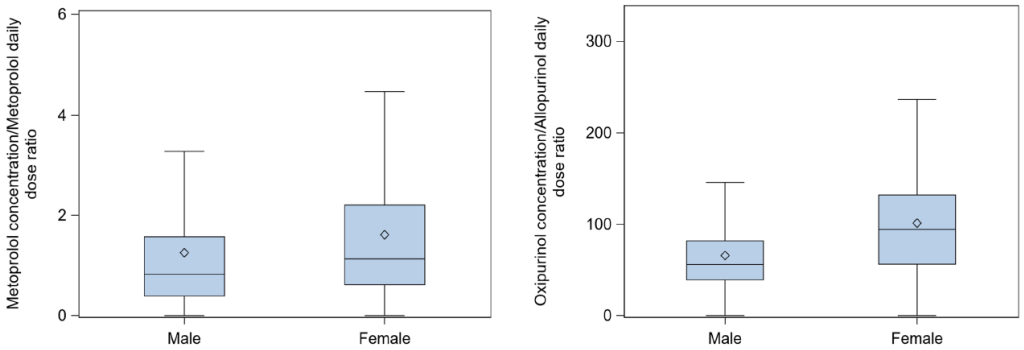


TABLE 2 Association between sex and metoprolol and oxypurinol concentrations in adjusted model.

	Metoprolol concentrations			Oxypurinol concentrations		
Effect	Estimate (SE)	*P* value	R^2 28.38	Estimate (SE)	*P* value	R^2 11.22
Sex (female)	0.350 (0.083)	**2.5×10^{-5}**	1.55	0.444 (0.196)	**0.0243**	0.67
Age	0.017 (0.004)	**0.0001**	1.35	0.042 (0.009)	**1.5×10^{-6}**	3.19
Daily dose	0.012 (0.001)	**4.0×10^{-68}**	25.48	0.005 (0.001)	**1.9×10^{-9}**	7.36

Hindi J, Pilon MO, et al. Clin Transl Sci. 2023; Online ahead of print.

Résumé de la dernière année – Principales publications/soumissions

- ALLO-MHI/LEVEL-PGx

TABLE 3 Association between variables of interest and metoprolol and oxypurinol concentrations.

	Metoprolol concentrations ($N = 701$)			Oxypurinol concentrations ($N = 328$)	
Effect	**Estimate (SE)**	***P* value**	**Effect**	**Estimate (SE)**	***P* value**
Sex (female)	0.292 (0.100)	**0.0037**	Sex (female)	0.237 (0.252)	0.3467
Daily dose	0.013 (0.001)	**7.4×10^{-62}**	Daily dose	0.007 (0.001)	**5.2×10^{-10}**
Weight	−0.007 (0.003)	**0.0076**	Weight	−0.014 (0.005)	**0.0034**
CYP2D6 genotype-inferred phenotype	−0.598 (0.060)	**6.8×10^{-22}**	eGFR	−0.015 (0.004)	**0.0007**
Age	0.013 (0.005)	**0.0061**	–	–	–
Use of CYP2D6 inhibitor	0.359 (0.121)	**0.0032**	–	–	–
–	–	–	Working status (full time)[a]	−0.394 (0.250)	0.1153
–	–	–	Working status (part time)[a]	−0.232 (0.260)	0.3730
–	–	–	Working status (other)[a]	−1.445 (0.377)	**0.0002**

Hindi J, Pilon MO, et al. Clin Transl Sci. 2023; Online ahead of print.

Résumé de la dernière année – Principales publications/soumissions

- ALLO-MHI/LEVEL-PGx

TABLE 4 Association between variables of interest and metoprolol and allopurinol daily dose.

Metoprolol daily dose ($N = 701$)			Allopurinol daily dose ($N = 328$)		
Effect	**Estimate (SE)**	***P* value**	**Effect**	**Estimate (SE)**	***P* value**
Sex (female)	−0.103 (0.075)	0.1696	Sex (female)	−0.061 (0.074)	0.4129
Waist girth	0.010 (0.002)	**2.8×10^{-7}**	Waist girth	0.004 (0.002)	**0.0212**
CYP2D6 genotype-inferred phenotype	0.112 (0.035)	**0.0015**	eGFR	0.005 (0.001)	**0.0001**
Height	−1.133 (0.350)	**0.0013**	–	–	–
Allergy to medication	0.120 (0.052)	**0.0218**	–	–	–
–	–	–	Use of diuretic	0.150 (0.053)	**0.0053**

Note: Stepwise model; intercepts for metoprolol daily dose: 4.934, oxypurinol daily dose: 4.359. Significant *p* values (<0.05) are highlighted in bold.

Abbreviations: eGFR, estimated glomerular filtration rate; SE, standard error.

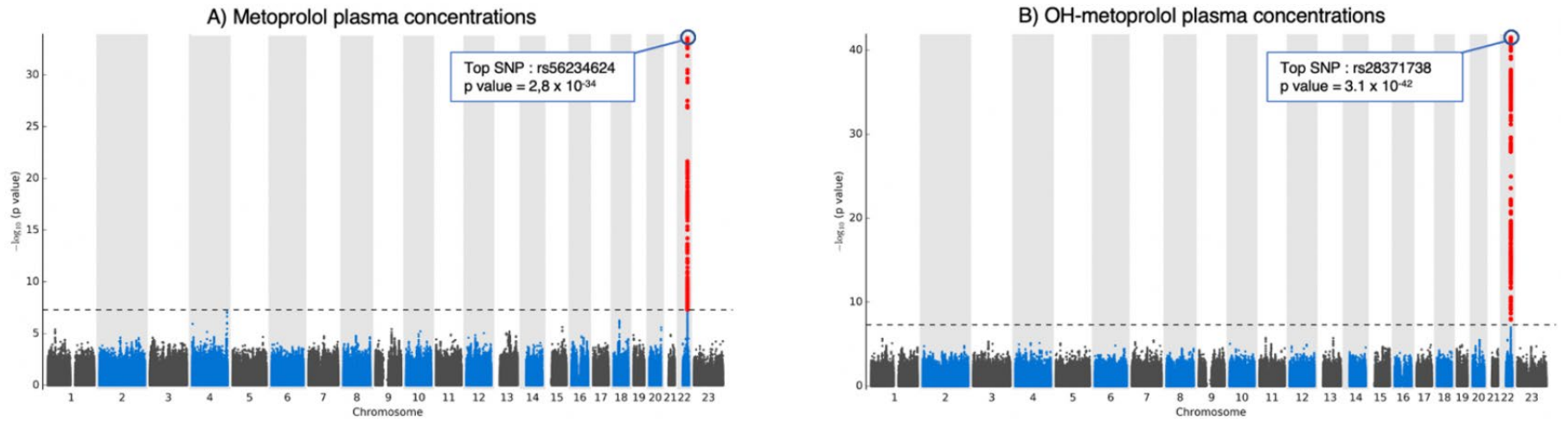
Hindi J, Pilon MO, et al. Clin Transl Sci. 2023; Online ahead of print.

Résumé de la dernière année – Principales publications/soumissions

- LEVEL-PGx

Pharmacogenomic markers of metoprolol and alpha-OH-metoprolol concentrations: A genome-wide association study

Figure 1 – Association between issues of interest and genotyped or imputed variants

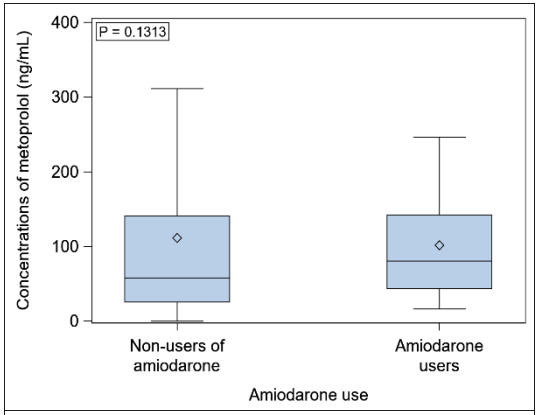


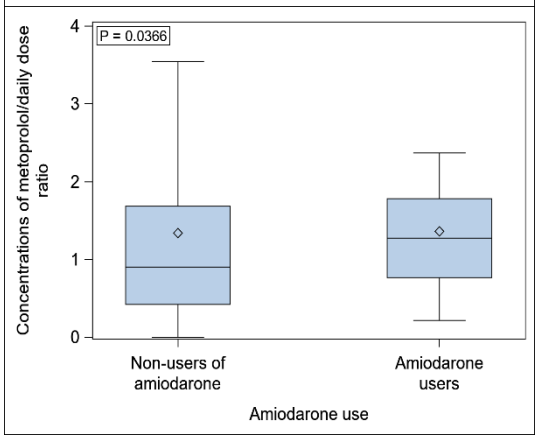
Laverdières J, et al. Soumis: Pharmacogenomics

Résumé de la dernière année – Principales publications/soumissions

- LEVEL-PGx

Impact of amiodarone use on metoprolol concentrations, α-OH-metoprolol concentrations, metoprolol dosing and heart rate: a cross-sectional study





Effect	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	Estimate (SE)	P value	Estimate (SE)	P value	Estimate (SE)	P value	Estimate (SE)	P value	Estimate (SE)	P value	Estimate (SE)	P value
Amiodarone	0.366 (0.233)	0.1155	0.353 (0.225)	0.1176	0.382 (0.222)	0.0860	**0.476 (0.183)**	**0.0095**	**0.446 (0.182)**	**0.0146**	**0.449 (0.181)**	**0.0132**
CYP2D6-inferred phenotype	-	-	**-0.505 (0.062)**	**1.4 x 10^{-15}**	**-0.511 (0.061)**	**2.9 x 10^{-16}**	**-0.631 (0.051)**	**5.0 x 10^{-33}**	**-0.634 (0.050)**	**1.3 x 10^{-33}**	**-0.630 (0.050)**	**1.1 x 10^{-33}**
Age	-	-	-	-	**0.016 (0.005)**	**0.0006**	**0.015 (0.004)**	**0.0001**	**0.012 (0.004)**	**0.0030**	**0.012 (0.004)**	**0.0029**
Female sex	-	-	-	-	**0.408 (0.094)**	**1.5 x 10^{-5}**	**0.404 (0.077)**	**2.0 x 10^{-7}**	**0.311 (0.081)**	**0.0001**	**0.299 (0.080)**	**0.0002**
Metoprolol daily dose	-	-	-	-	-	-	**0.013 (0.001)**	**1.4 x 10^{-85}**	**0.013 (0.001)**	**3.1 x 10^{-88}**	**0.013 (0.001)**	**1.3 x 10^{-89}**
Weight	-	-	-	-	-	-	-	-	**-0.008 (0.002)**	**0.0003**	**-0.008 (0.002)**	**0.0003**
Use of moderate-strong CYP2D6 inhibitors	-	-	-	-	-	-	-	-	-	-	**0.386 (0.098)**	**0.0001**

Robert S, et al. Soumis: Br J Clin Pharmacol

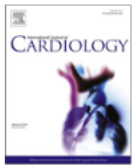
Résumé de la dernière année - Collaborations

International Journal of Cardiology 370 (2023) 300–308

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Optimization of pharmacotherapies for ambulatory patients with heart failure and reduced ejection fraction is associated with improved outcomes

Marilyne Jarjour[a,b,1], Jacinthe Leclerc[c,d,1], Nadia Bouabdallaoui[b,1], Charaf Ahnadi[e,1], Denis Brouillette[f,1], Simon de Denus[f,1], Annik Fortier[g,1], Patrick Garceau[b,1], Geneviève Giraldeau[b,1], Serge Lepage[e,1], Mark Liszkowski[b,1], Eileen O'Meara[b,1], Marie-Claude Parent[b,1], Normand Racine[b,1], Maxime Tremblay-Gravel[b,1], Michel White[b,1], Jean-Lucien Rouleau[b,1], Anique Ducharme[b,*]

ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 2997–3008
Published online 23 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14026

ORIGINAL ARTICLE

Pharmacogenomic study of heart failure and candesartan response from the CHARM programme

Marie-Pierre Dubé[1,2,3*], Olympe Chazara[4], Audrey Lemaçon[1,2,3], Géraldine Asselin[1,2], Sylvie Provost[1,2], Amina Barhdadi[1,2], Louis-Philippe Lemieux Perreault[1,2], Ian Mongrain[1,2], Quanli Wang[4], Keren Carss[4], Dirk S. Paul[4], Jonathan W. Cunningham[5], Jean Rouleau[1,3], Scott D. Solomon[5], John J.V. McMurray[6], Salim Yusuf[7], Chris B. Granger[8], Carolina Haefliger[4], Simon de Denus[1,2,9] and Jean-Claude Tardif[1,3*]

Study of the effect of sex on drugs dosing, concentrations and pharmacogenomics

- **Specific objectives**
  - To identify drug doses and drug or metabolite concentrations that differ between females and males;
  - To identify and characterize the clinical and genetic predictors of drug concentrations and dosing in females and males, and to assess whether they are sufficient to explain any observed sex differences;
  - To identify individuals with undetectable drug concentrations, as a marker of drug nonadherence

Study of the effect of sex on drugs dosing, concentrations and pharmacogenomics

- **Study design**
  - Cross sectional study of 10 000 participants from the MHI Hospital Cohort treated with 48 commonly used drugs at baseline.
- **Study population.**
  1. Male or female of European ancestry aged ≥ 18 years
  2. Use of at least one of the study drugs at the time of plasma collection
  3. Availability at least one adequate plasma aliquot.

Drug class	Agent or active metabolite
Lipid-lowering agents	Atorvastatin/2-hydroxy-atorvastatin acid, rosuvastatin, pravastatin, simvastatin/simvastatin-hydroxy acid, ezetimibe/ezetimibe-glucuronide
Beta-blockers	Metoprolol, bisoprolol, atenolol, carvedilol/4-hydroxyphenyl-carvedilol
Calcium channel blockers	Amlodipine, diltiazem/deacetyl-diltiazem, nifedipine
Antidiabetic agents	Metformin, gliclazide, glyburide (glibenclamide), sitagliptin, saxagliptin/5-hydroxysaxagliptin
Antiplatelets and anticoagulants	Warfarin, rivaroxaban, apixaban, dabigatran, clopidogrel and metabolite
ACE inhibitors	Ramipril/ramiprilat, perindopril/perindoprilat, trandolapril/trandolaprilat, enalapril/enalaprilat
ARBs	Candesartan, irbesartan, telmisartan, valsartan, sacubitril/LBQ657
Diuretics	Furosemide/furosemide glucuronide, HCTZ, indapamide, spironolactone/canrenone, eplerenone
Antiarrhythmic agents	Amiodarone/N-desethylamiodarone, sotalol
Antidepressants	Citalopram/N-desmethyl-citalopram, venlafaxine/O-desmethyl-venlafaxin
Proton pump inhibitors	Pantoprazole, omeprazole/esomeprazole, dexlansoprazole/lansoprazole
Others	Pregabalin, prednisone/prednisolone

CIHR IRSC

Study of the effect of sex on drugs dosing, concentrations and pharmacogenomics

- Progression du projet
  - La révision/collecte des dossiers des 10 000 patients éligibles a été complétée (02/2022).
    - Données transférées à Statgen (04/2022)
    - Nettoyage des données des données cliniques (05/2023)
  - Génotypage des 10 000 patients complétés sur la plateforme ADME MassARRAY (Agena Bioscience, San Diego, CA) (03/2022)
    - Nettoyage des données génétiques complétées
    - Inferrage des phénotypes (05/2023)
  - Analyses plasmatiques des concentrations de médicaments complétés pour les 4000 premiers patients (05/2023)
    - Échantillons 4001-5000 transférés et présentement en quantification (05/2023).

Étudiants gradué.e.s:
Jessica Hindi; Marc-Olivier Pilon.

Study of the effect of sex on drugs dosing, concentrations and pharmacogenomics

- Progression du projet
  - Préparation article “Méthodologie et population à l’étude” (mise à jour des tableaux en cours puis prêt pour soumission)

Study of the effect of sex on drugs dosing, concentrations and pharmacogenomics

- A venir en 2023-2024:
  - Déterminants des doses des 48 médicaments étudiés.
  - Identification de la prévalence des haplotypes/génotypes/phénotypes inférés menant à une action - « *actionable* » - selon CPIC dans une population atteinte de/à haut risque de maladie CV
    - Prévalence des haplotypes/génotypes/phénotypes inférés menant à une action
    - Prévalence chez des patients prenant une combinaison médicament-pharmacogène
    - **Justification**: Connaître la prévalence de cette information chez une population spécifique afin d'identifier 1) utilisation potentielle et 2) la possibilité d'éventuellement transférer cette information de la Biobanque au dossier clinique lorsque cliniquement indiqué

Autres projets en cours

Genome-wide study of disease progression in patients with established heart failure

HERMES- progression consortium

LEVEL-PGx-ALLO-MHI – Machine learning

Revue systématique – Poids et insuffisance cardiaque – accepté pour publication (05/2023)

TOPCAT-CHIP:

- Contrat signé (09/2021)
- Échantillons reçus (11/2021)
- SAP de selection des échantillons complété (02/2022)
- Analyses été 2023

ATHENA/TOPCAT canrenone concentrations predictors

- Analyses terminées – manuscrit en préparation