

L'effet des caractéristiques des donneurs de sang sur les receveurs de transfusions de globules rouges

8 novembre 2017

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Conflits d'intérêts

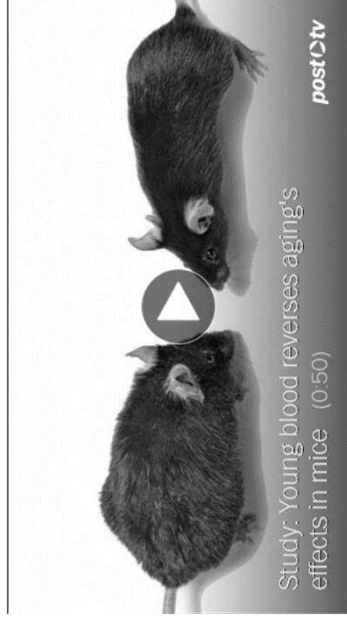
- Aucun.
- Sources de financement



Ad

Health & Science

New studies show that young blood reverses the effects of aging when put into older mice



A blood-based protein that can rejuvenate the hearts of aging mice, has a similar effect on the mice's brain and skeletal muscle function, according to scientists at Harvard University. (Photo by Tony Wyss-Coray.) (Reuters)

Young blood to be used in ultimate rejuvenation trial

- > [20 August 2014 by Helen Thomson](#)
- > [Magazine issue 2983. Subscribe and save](#)
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Back To Basics: Blood Transfusion May Treat Ebola Virus Disease

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The doctor who survived Ebola Virus Disease because of blood transfusion

(Photo : nbcnews.com) The d

Le sang des jeunes et des femmes moins bon pour la transfusion?

PUBLIÉ LE VENDREDI 15 JUILLET 2016

MIS À JOUR LE DIMANCHE 17 JUILLET 2016



Objectifs

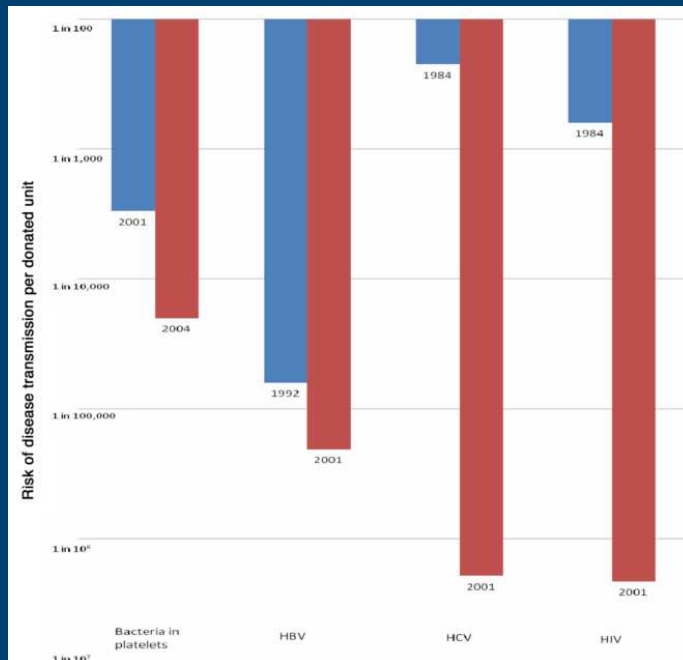
- Comprendre comment les caractéristiques des donneurs de sang pourraient influencer l'issue clinique des receveurs;
- Présenter une stratégie d'étude des caractéristiques des donneurs de sang
- Présenter les résultats d'une étude récente Canadienne qui suggère un effet des caractéristiques des donneurs de sang sur la survie des receveurs

Pourquoi étudier les donneurs??

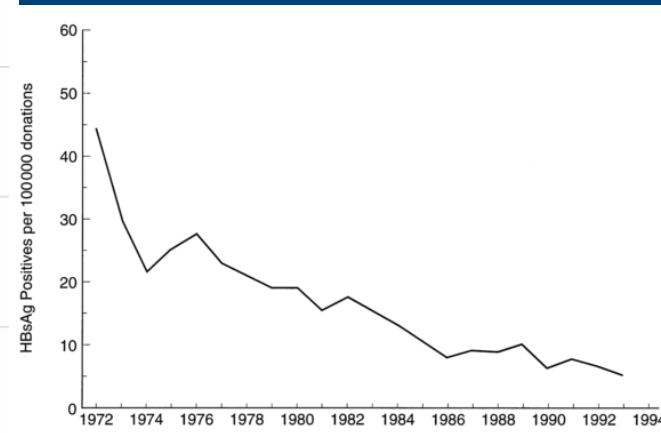


Historiquement cible principale pour l'amélioration des issues cliniques

- Effets du dépistage des donneurs



BLOOD, 9 APRIL 2009 VOLUME 113, NUMBER 15



Rationelle brève

- Donor age may affect RBCs
 - Decreased erythrocytes precursors
 - Increased DNA damage (increased oncogenic risk)
 - Changes in cell membrane compositions (decreased phospholipid content, senescence of surface antigen)
 - Increased cytokines levels (risk of infections)
 - Many other unknown factors
- Sex affects RBCs
 - Changes in response to adrenaline (decreased O₂ affinity, increased membrane rigidity in females).
 - Different composition (hormonal, antigens...)

Cancer Control 1998;5(2 Suppl 1):17–21.

Exp Gerontol 1999;34(1):47–57.

Blood Rev 2014;

Aging (Albany NY) 2011;3(6):643–56.

Clin Hemorheol Microcirc 2003;28(2):89–98.

Blood 2001;98(7):2043–51.

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Contents lists available at [ScienceDirect](#)

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com



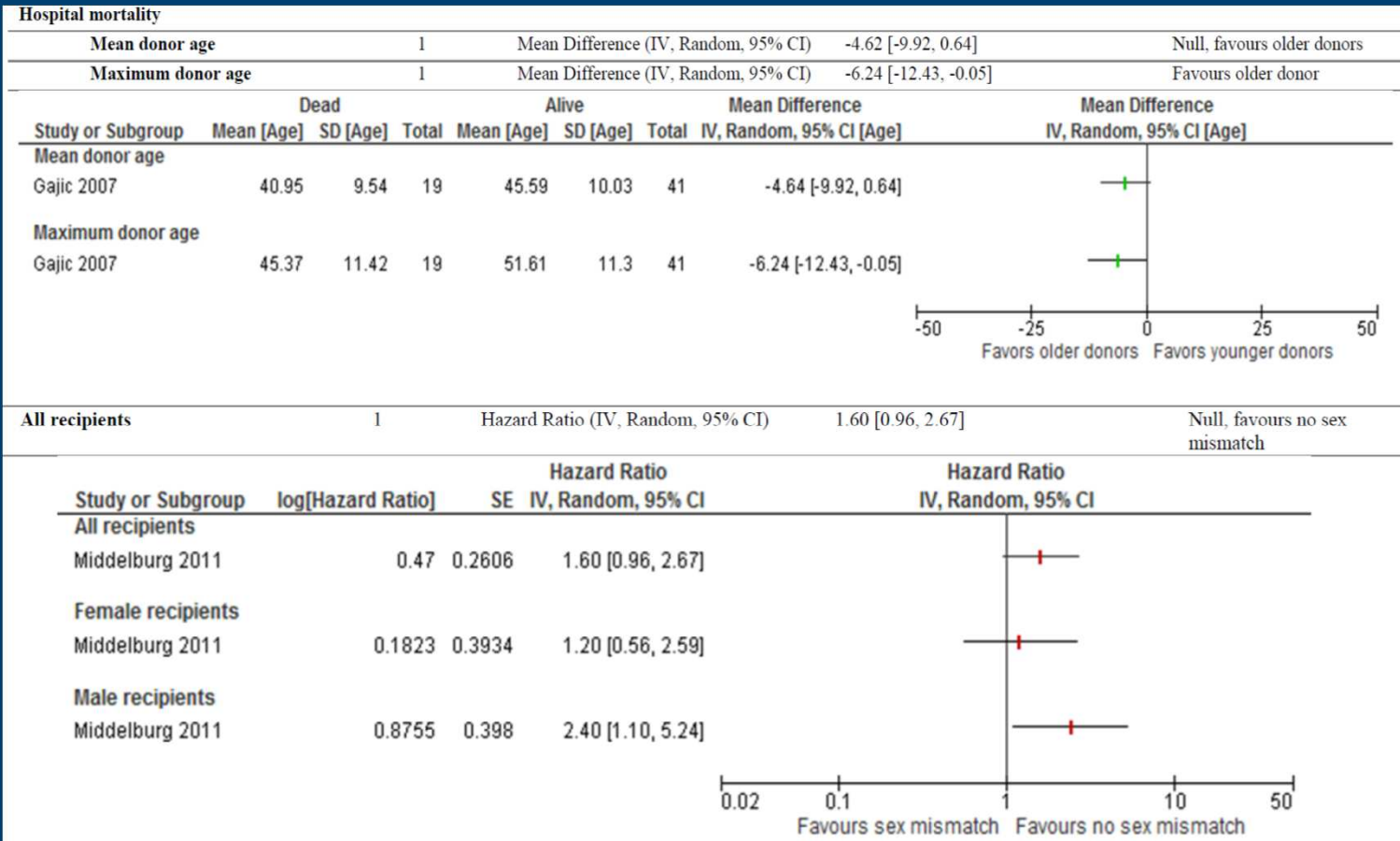
Effect of Blood Donor Characteristics on Transfusion Outcomes: A Systematic Review and Meta-Analysis

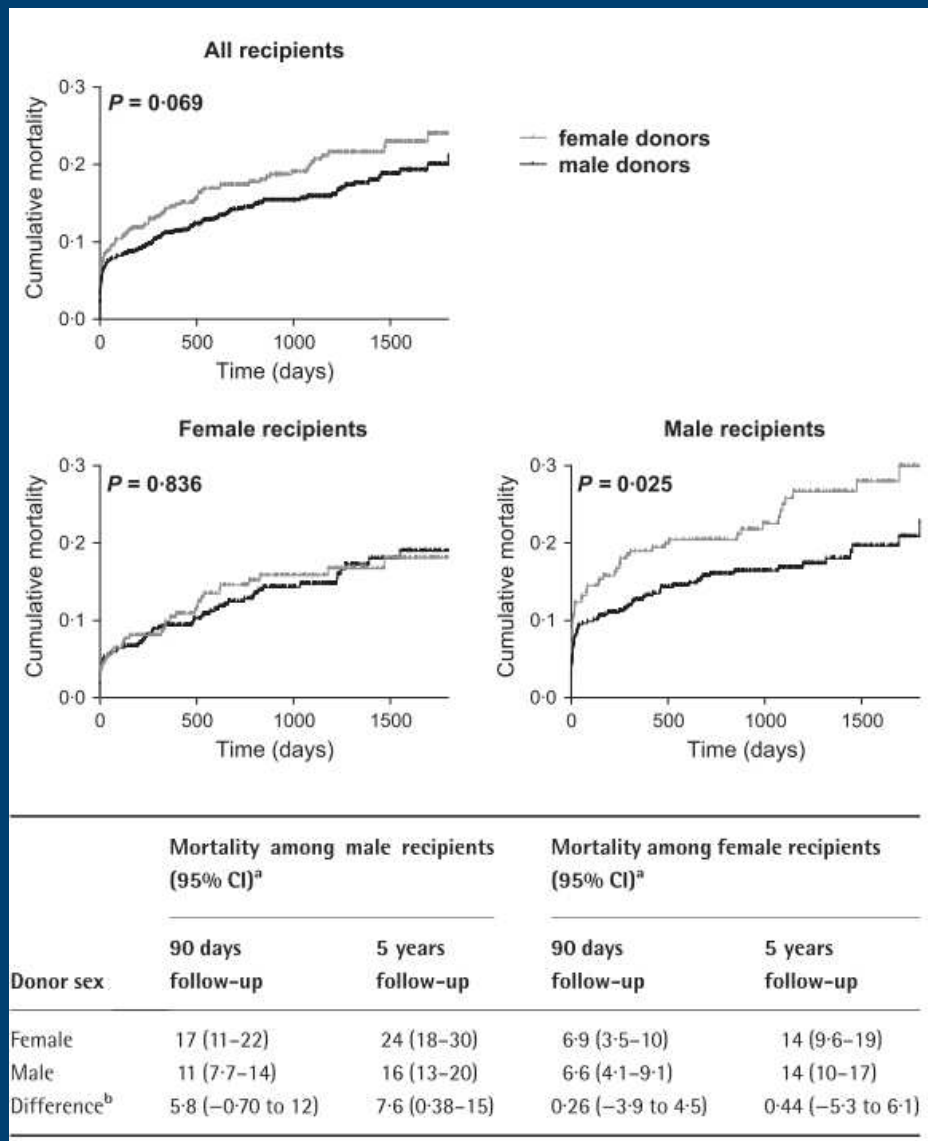


Michaël Chassé ^a, Lauralyn McIntyre ^b, Shane W. English ^b, Alan Tinmouth ^c, Greg Knoll ^b, Dianna Wolfe ^d,
Kumanan Wilson ^e, Nadine Shehata ^f, Alan Forster ^g, Carl van Walraven ^h, Dean A. Fergusson ^{i,*}

Summary of the review

- Based on poor quality evidence:
 - Donor positive antileukocyte antibodies (TRALI)
 - Female donor to male recipients (survival)
 - HLA-DR selected RBC transfusion (transplantation outcome)
 - Donor RBC antigen selection (alloimmunization)
- May affect RBC transfusion outcome.





Middelburg, Transfusion, 2011

BMJ Open Clinical effects of blood donor characteristics in transfusion recipients: protocol of a framework to study the blood donor–recipient continuum

Michaël Chassé,¹ Lauralyn McIntyre,¹ Alan Tinmouth,¹ Jason Acker,²
Shane W English,^{1,3} Greg Knoll,¹ Alan Forster,⁴ Nadine Shehata,⁵
Kumanan Wilson,^{1,6,7} Carl van Walraven,¹ Robin Ducharme,^{1,7} Dean A Fergusson¹

Chassé, BMJ Open, 2015

Methode

- Design: Étude de cohorte longitudinale
- Population:
 - Tous les patients
 - Recevant au moins une transfusion allogénique de globules rouges
 - Dans 4 hôpitaux(The Ottawa Hospital – General Campus, The Ottawa Hospital – Civic Campus, The University of Ottawa Heart Institute, and The Ottawa Hospital – Riverside Campus)
- Source des données
 - Canadian Blood Services (Données donneur)
 - The Ottawa Hospital DataWarehouse (données transfusionnelles, résultats de cultures, comorbidités)
 - ICES (Registered Person Database, Ontario Cancer Registry, CIHI-DAD)

L'infrastructure

Canadian Blood Services

Hospital Datawarehouse

Data analysis

Donor

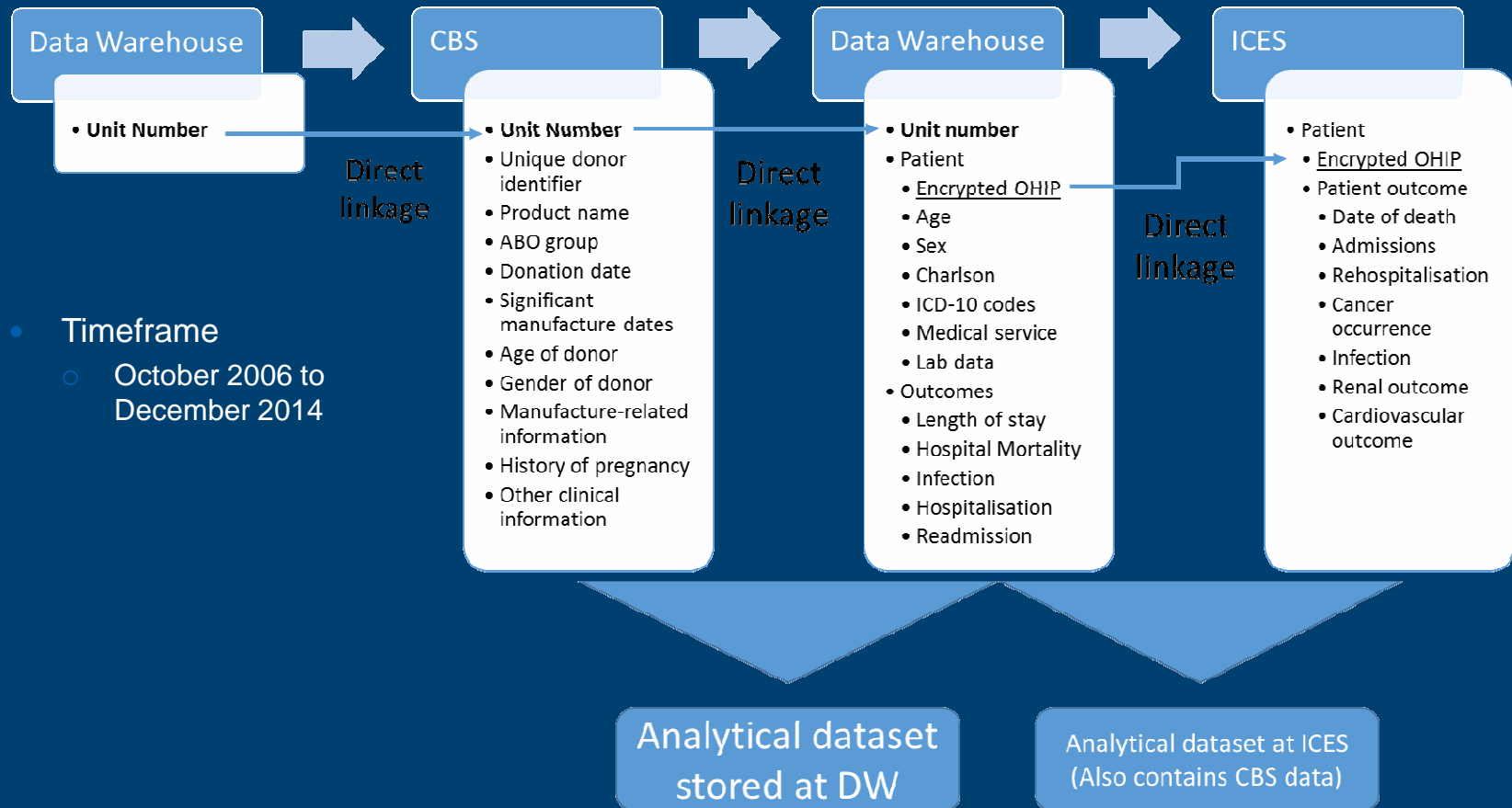
Patient

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IM

L'infrastructure



Analyses

- Analyses principales
 - Extended cox model (Based on the Anderson & Gill model)
 - Transfusions multiples
 - Mesures répétées dans le temps
 - Donneurs multiples
 - Caractéristiques différentes des donneurs
 - Ajustement pour les caractéristiques des receveurs
 - Expositions principales: Âge et Sexe des donneurs
 - Issue primaire: Survie



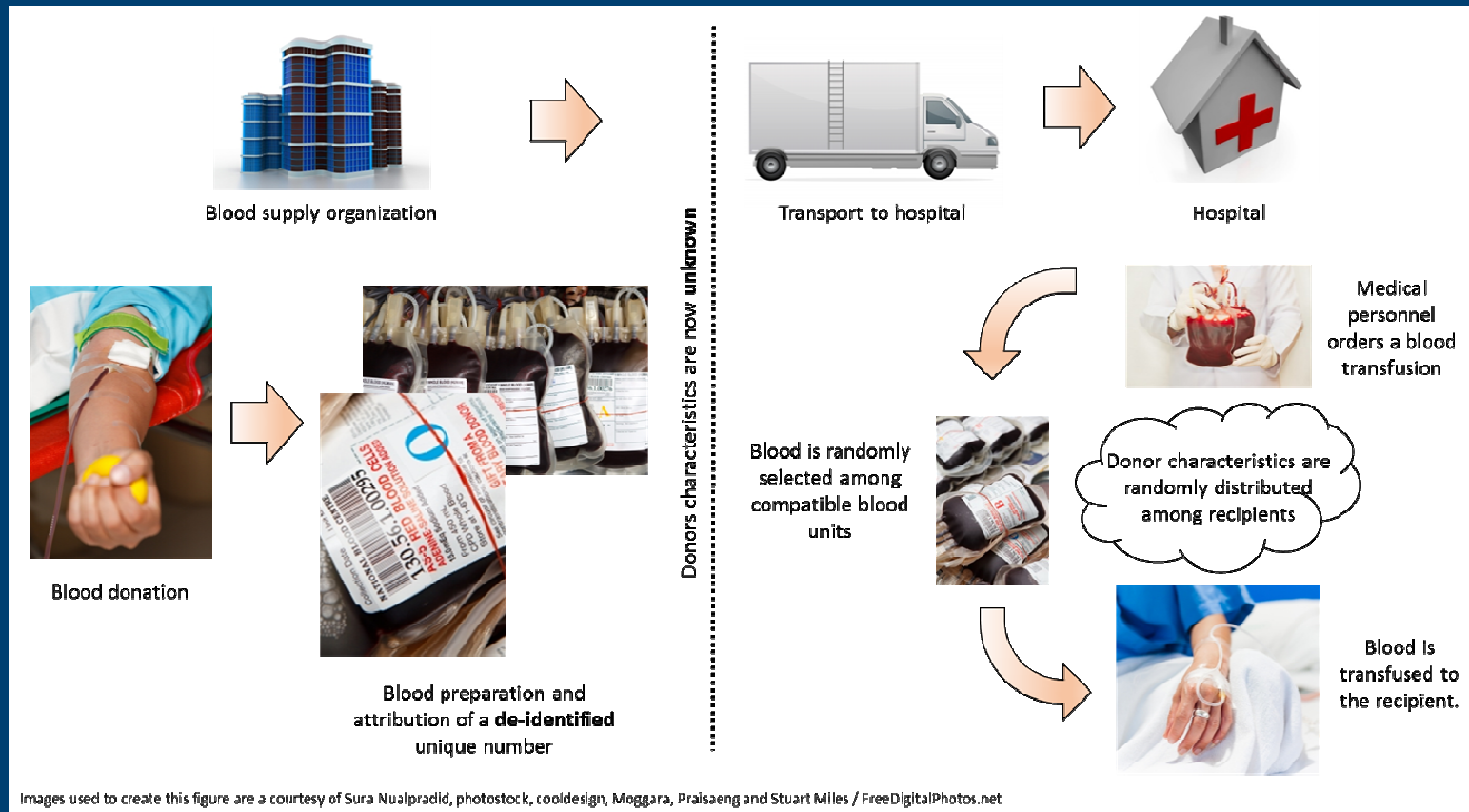
2009

2010

2011

ID	Start	End	Cum M	Cum F	Total	Cov1	Censor
1	0	30	0	1	1	A	0
1	30	40	0	2	2	A	0
1	40	100	1	2	3	A	1
2	0	20	1	0	1	B	0
2	20	75	1	1	2	B	0
...

Facteurs confondants?



Research

JAMA Internal Medicine Published online July 11, 2016

Original Investigation

Association of Blood Donor Age and Sex With Recipient Survival After Red Blood Cell Transfusion

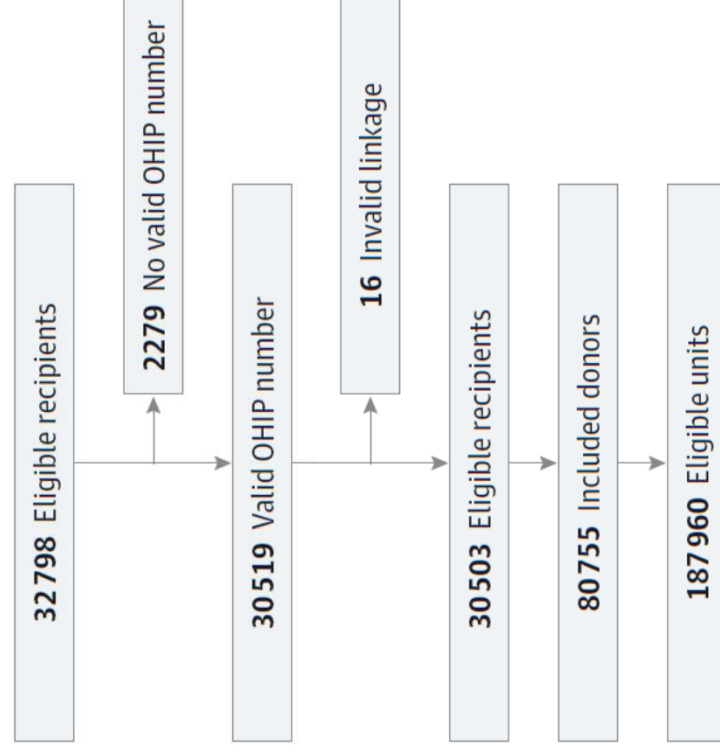
Michaël Chassé, MD, PhD, FRCPC; Alan Tinmouth, MD, MSc, FRCPC; Shane W. English, MD, MSc, FRCPC;
Jason P. Acker, MBA, PhD; Kumanan Wilson, MD, FRCPC; Greg Knoll, MD, MSc, FRCPC;
Nadine Shehata, MD, MSc, FRCPC; Carl van Walraven, MD, MSc, FRCPC; Alan J. Forster, MD, MSc, FRCPC;
Timothy Ramsay, PhD; Lauralyn A. McIntyre, MD, MSc, FRCPC; Dean A. Fergusson, MHA, PhD

Chassé, JAMA Int Med, 2016

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Figure 1. Flowchart of the Study Cohort



Receveurs

Table 1. Recipient Characteristics at the Time of First Transfusion

Variable	Value (n = 30 503)
Age, y	
Mean (SD)	66.2 (18.2)
Median (IQR)	69.0 (56.0-80.0)
Male age, y	
Mean (SD)	66.6 (17.2)
Median (IQR)	69.0 (58.0-79.0)
Female age, y	
Mean (SD)	65.8 (19.1)
Median (IQR)	69.0 (54.0-81.0)
Sex, No. (%)	
Male	14 597 (47.9)
Female	15 906 (52.1)
ABO blood group, No. (%)	
A negative	1943 (6.4)
A positive	9872 (32.4)
AB negative	202 (0.7)
AB positive	1037 (3.4)
B negative	497 (1.6)
B positive	3153 (10.3)
O negative	2207 (7.2)
O positive	11 450 (37.5)
No result available	16 (0.1)
Variable results	90 (0.3)

First available Charlson Comorbidity Index, No. (%)

0	8812 (28.9)
1-2	8155 (26.7)
3-4	4436 (14.5)
≥5	6314 (20.7)
Not available	2786 (9.1)
Comorbid conditions, No./total No. (%)^a	
Cardiac disease	2521/27 717 (9.1)
Congestive heart failure	3313/27 717 (12.0)
Peripheral vascular disease	2079/27 717 (7.5)
Cerebrovascular disease	818/27 717 (3.0)
Dementia	842/27 717 (3.0)
COPD	1820/27 717 (6.6)
Connective tissue disease	308/27 717 (1.1)
Peptic ulcer disease	1020/27 717 (3.7)
Mild liver disease	767/27 717 (2.8)
Moderate or severe liver disease	495/27 717 (1.8)
Diabetes with no organ damage	2448/27 717 (8.8)
Diabetes with organ damage	4830/27 717 (17.4)
Hemiplegia	400/27 717 (1.4)
Moderate or severe renal failure	2205/27 717 (8.0)
Cancer without metastases	7246/27 717 (26.1)
Cancer with metastases	3164/27 717 (11.4)
Human immunodeficiency virus	92/27 717 (0.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

^a A total of 2786 patients had no comorbid conditions data collected.

Donneurs

Table 2. Donor Characteristics at the Time of First Donation

Variable	Value (n = 80 755)
Sex, No. (%)	
Male	41 427 (51.3)
Female	39 328 (48.7)
Age, y	
Mean (SD)	40.4 (14.5)
Median (IQR)	42.0 (27.0-52.0)
Age group, y, No. (%)	
17-19.9	8643 (10.7)
20-29.9	14 787 (18.3)
30-39.9	12 461 (15.4)
40-49.9	19 178 (23.8)
50-59.9	18 485 (22.9)
60-69.9	6903 (8.6)
≥70	298 (0.4)
No. of previous whole blood donations	
Mean (SD)	12.7 (19.0)
Median (IQR)	5 (1-17)
Donor ABO blood group, No./total No. (%)	
A negative	6258 (7.8)
A positive	23 782 (29.5)
AB negative	687 (0.9)
AB positive	1869 (2.3)
B negative	1683 (2.1)
B positive	6874 (8.5)
O negative	8584 (10.6)
O positive	31 018 (38.4)

Abbreviation: IQR, interquartile range.

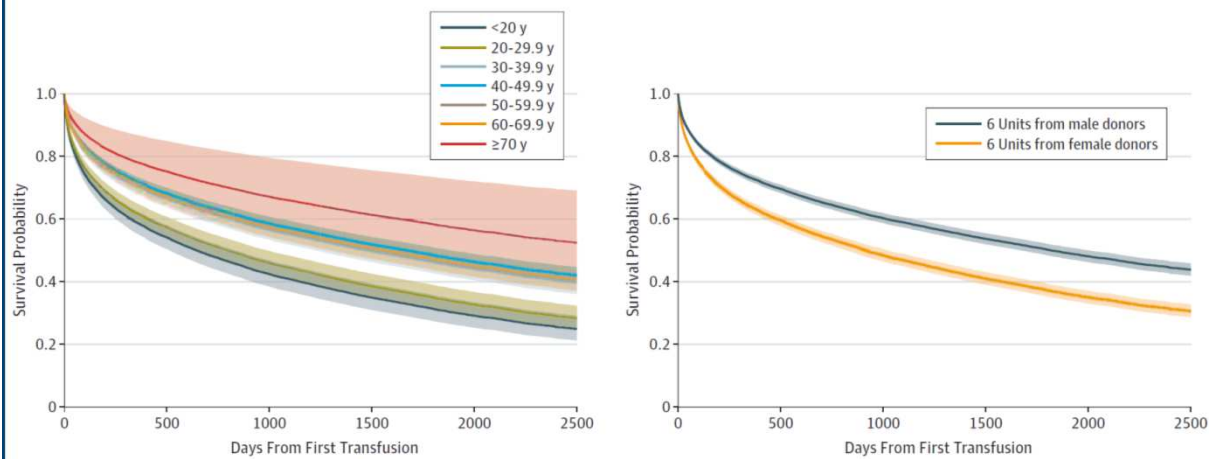
Groupes comparables?

	Donor age < 30	Donor age ≥ 30
Recipient age		
Mean (SD)	64.9 (22.2)	66.5 (19.0)
Female recipients (%)	54.4	54.9
Charlson's Index		
0 (%)	27.3	25.4
1-2 (%)	18.5	18.8
3-4 (%)	10.9	11.6
5 + (%)	14.8	15.9
N/A (%)	28.5	28.4

	Female donors	Male donors
Recipient age		
Mean (SD)	66.5 (20.3)	66.0 (19.6)
Female recipients (%)	55.0	55.5
Charlson's Index		
0 (%)	25.8	26.3
1-2 (%)	18.5	18.6
3-4 (%)	11.6	11.6
5 + (%)	15.5	15.5
N/A (%)	28.5	28.0

Résultats principaux

Figure 2. Patient Survival According to Donor Age and Sex Using a Base Case of 6 Total Transfusions (Study Mean) Over the Study Period Between 2006 and 2013



This figure represents the survival of a recipient of 6 units of only one donor characteristic vs the other at baseline at the study mean recipient age and median Charlson Score.

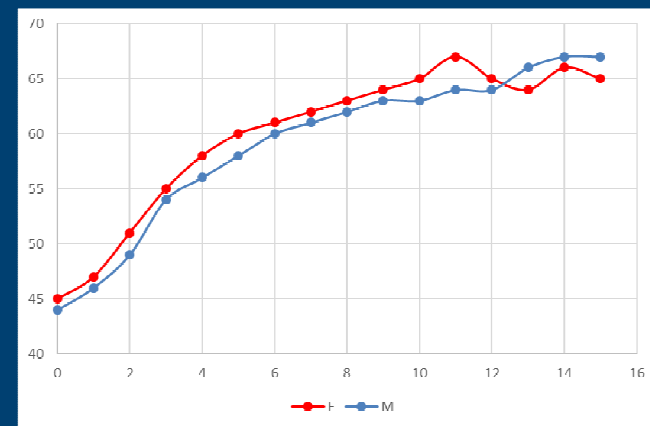
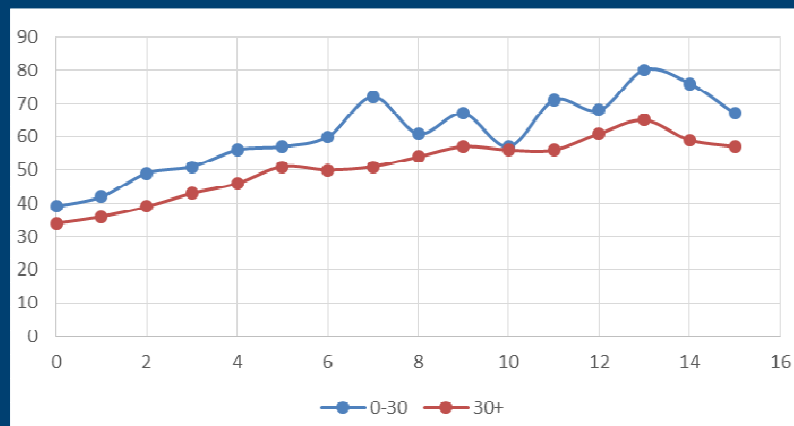
Table 3. Unadjusted and Adjusted Patient Survival According to Donor Age and Sex, per Additional Unit Transfused

Variable	HR (95% CI)	
	Unadjusted	Adjusted ^a
Donor age, y		
17-19.9	1.14 (1.12-1.16)	1.08 (1.06-1.10)
20-29.9	1.06 (1.04-1.08)	1.06 (1.04-1.09)
30-39.9	1.01 (0.99-1.03)	1.01 (0.99-1.03)
40-49.9	1 [Reference]	1 [Reference]
50-59.9	1.00 (0.99-1.02)	1.01 (0.99-1.02)
60-69.9	1.02 (1.00-1.03)	1.01 (0.99-1.03)
≥70.0	0.89 (0.83-0.95)	0.96 (0.89-1.03)
Donor sex		
Male	1 [Reference]	1 [Reference]
Female	1.08 (1.07-1.09)	1.08 (1.06-1.09)

Abbreviation: HR, hazard ratio.

^a Adjusted for recipient age, recipient sex, and Charlson Comorbidity Index.

Proportion of patients dying for patients receiving only female or only “young” RBCs



Interprétation

- Nous avons observé une réduction de la survie après la transfusion de globules rouges:
 - Donneurs de sexe féminin
 - Donneurs plus jeunes
- Nécessite confirmation:
 - ARR 6.2% par an; 95% CI 5.4% to 7.0% à la moyenne de l'étude de 6 transfusions
 - Number Needed to Treat (NNT): 16

Autres résultats préliminaires

- Cancer

		Unadjusted			Adjusted		
		HR	LCI	UCI	HR	LCI	UCI
Donor age (years)	17 – 19.9	1.07	1.03	1.11	1.06	1.03	1.10
	20 – 29.9	1.05	1.01	1.08	1.05	1.01	1.08
	30 – 39.9	1.05	1.00	1.07	1.04	0.99	1.07
	40 – 49.9	0.99	0.97	1.01	0.99	0.97	1.01
	50 – 59.9	0.99	0.97	1.02	0.99	0.97	1.02
	60 – 69.9	1.02	0.98	1.06	1.02	0.98	1.06
	≥ 70.0	0.93	0.81	1.09	0.96	0.83	1.10
Donor age (years)	< 30	1.07	1.05	1.09	1.06	1.04	1.09
	≥ 30	1.00	0.99	1.00	1.00	1.00	1.00
Donor sex	Female	1.03	1.01	1.05	1.03	1.01	1.04
	Male	0.99	0.98	1.00	1.00	0.98	1.01

Autres résultats préliminaires

- Infarctus du myocarde

		Unadjusted			Adjusted*		
		HR	LCI	UCI	HR	LCI	UCI
Donor age (years)	17 – 19.9	1.04	0.97	1.12	1.04	0.97	1.12
	20 – 29.9	0.98	0.91	1.05	0.98	0.90	1.05
	30 – 39.9	1.06	0.99	1.14	1.06	0.99	1.14
	40 – 49.9	1.00	0.95	1.05	1.00	0.95	1.05
	50 – 59.9	1.00	0.96	1.05	1.00	0.95	1.05
	60 – 69.9	0.98	0.90	1.06	0.99	0.92	1.07
	≥ 70.0	0.80	0.58	1.11	0.79	0.57	1.09
Donor age (years)	< 30	1.02	0.96	1.07	1.01	0.96	1.07
	≥ 30	1.00	0.99	1.01	1.00	0.99	1.01
Donor sex	Female	1.01	0.98	1.05	1.01	0.98	1.05
	Male	0.99	0.97	1.02	1.00	0.98	1.01

Autres résultats préliminaires

- SARM

		Unadjusted			Adjusted*		
		HR	LCI	UCI	HR	LCI	UCI
Donor age (years)	17 – 19.9	0.97	0.92	1.03	0.97	0.91	1.01
	20 – 29.9	1.11	1.05	1.18	1.11	1.06	1.17
	30 – 39.9	1.01	0.95	1.07	1.01	0.95	1.07
	40 – 49.9	0.99	0.96	1.02	0.99	0.98	1.03
	50 – 59.9	1.00	0.97	1.04	1.00	0.97	1.04
	60 – 69.9	0.99	0.934	1.05	0.99	0.94	1.05
	≥ 70.0	1.06	0.90	1.24	1.04	0.89	1.22
Donor age (years)	< 30	1.07	1.03	1.11	1.07	1.03	1.11
	≥ 30	1.00	0.99	1.01	1.00	0.99	1.01
Donor sex	Female	1.05	1.02	1.07	1.04	1.02	1.07
	Male	0.99	0.97	1.00	0.99	0.97	1.01

Autres résultats préliminaires

- C Difficile

		Unadjusted			Adjusted*		
		HR	LCI	UCI	HR	LCI	UCI
Donor age (years)	17 – 19.9	1.07	1.02	1.12	1.07	1.02	1.12
	20 – 29.9	1.09	1.03	1.15	1.09	1.04	1.15
	30 – 39.9	1.00	0.94	1.06	1.00	0.94	1.06
	40 – 49.9	0.98	0.95	1.02	0.98	0.95	1.02
	50 – 59.9	1.00	0.96	1.04	1.00	0.97	1.03
	60 – 69.9	1.05	0.99	1.11	1.05	1.00	1.10
	≥ 70.0	1.09	0.94	1.27	1.09	0.95	1.24
Donor age (years)	< 30	1.08	1.05	1.11	1.08	1.05	1.11
	≥ 30	1.00	1.00	1.01	1.01	1.00	1.01
Donor sex	Female	1.05	1.03	1.06	1.05	1.02	1.08
	Male	0.99	0.99	1.00	1.00	0.98	1.01

Limitations

- Il ne s'agit pas d'une preuve définitive que le sexe ou l'âge est la cause du changement de survie observé
 - Mécanismes inconnus
 - Tout ce qui est potentiellement associé à l'âge ou au sexe pourrait être "causal"
- Risque de facteurs confondants résiduels?
 - Potentiellement limit (allocation quasi-aléatoire, aveugle...)
- Statistiques complexes
- Effet non homogène entre les sous-groupes
 - Mais répété par d'autres
- Effet dose-réponse mais
 - Effet non linéaire (effet minimal lorsque peu de transfusions?)

Depuis...

- 3 publications
 - Desmarets et al. Transfusion 2016
 - Edgren et al. JAMA IM. 2017
 - Caram-Deelder. JAMA 2017

TRANSFUSION COMPLICATIONS

Effect of storage time and donor sex of transfused red blood cells on 1-year survival in patients undergoing cardiac surgery: an observational study

Maxime Desmarests,¹ Laurent Bardiaux,² Eric Benzenine,³ Alain Dussaucy,⁴ Delphine Binda,¹ Pierre Tiberghien,⁵ Catherine Quantin,^{3,6,7} and Elisabeth Monnet^{1,8}

- No effect
 - Manque franc de puissance pour l'effet attendu
 - Analyse non optimale

JAMA Internal Medicine | Original Investigation

Association of Donor Age and Sex With Survival of Patients Receiving Transfusions

Gustaf Edgren, MD, PhD; Henrik Ullum, MD, PhD; Klaus Rostgaard, MSc; Christian Erikstrup, MD, PhD; Ulrik Sartipy, MD, PhD; Martin J. Holzmann, MD, PhD; Olof Nyrén, MD, PhD; Henrik Hjalgrim, MD, PhD

- Ont reproduit nos analyses
 - Et nos résultats!
- Ont rajouté multiples transformations statistiques
 - Atténuation franche de l'effet

Table 2. Hazard Ratios of Death in Association With Number of Red Blood Cell Transfusions From Donors of Different Age and Sex

Characteristic	Red Blood Cell Units, No. (%) ^a	Hazard Ratio (95% CI) ^b		
		Unadjusted Model ^c	Model 1 ^c	Model 2 ^c
Unrestricted follow-up ^e				
Donor age, y				
<20	126 847 (1.9)	1.10 (1.09-1.10)	1.04 (1.03-1.04)	1.01 (1.00-1.01)
20-29	1 104 248 (16.3)	1.03 (1.03-1.03)	1.02 (1.02-1.02)	0.99 (0.99-1.00)
30-39	1 464 872 (21.6)	1.02 (1.02-1.02)	1.00 (1.00-1.00)	0.99 (0.99-1.00)
40-49	1 889 084 (27.9)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
50-59	1 600 320 (23.6)	1.02 (1.02-1.02)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
60-69	578 194 (8.5)	1.02 (1.02-1.02)	1.00 (1.00-1.01)	1.01 (1.01-1.02)
≥70	3238 (0.0)	0.86 (0.84-0.88)	0.85 (0.83-0.87)	0.96 (0.91-1.01)
Donor sex				
Female	2 762 781 (40.8)	1.04 (1.04-1.04)	1.01 (1.01-1.01)	1.00 (1.00-1.00)
Male	4 004 022 (59.2)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

Edgren G. et al. JAMA Intern Med. Published online April 24, 2017

Research

JAMA | **Original Investigation**

Association of Blood Transfusion From Female Donors With and Without a History of Pregnancy With Mortality Among Male and Female Transfusion Recipients

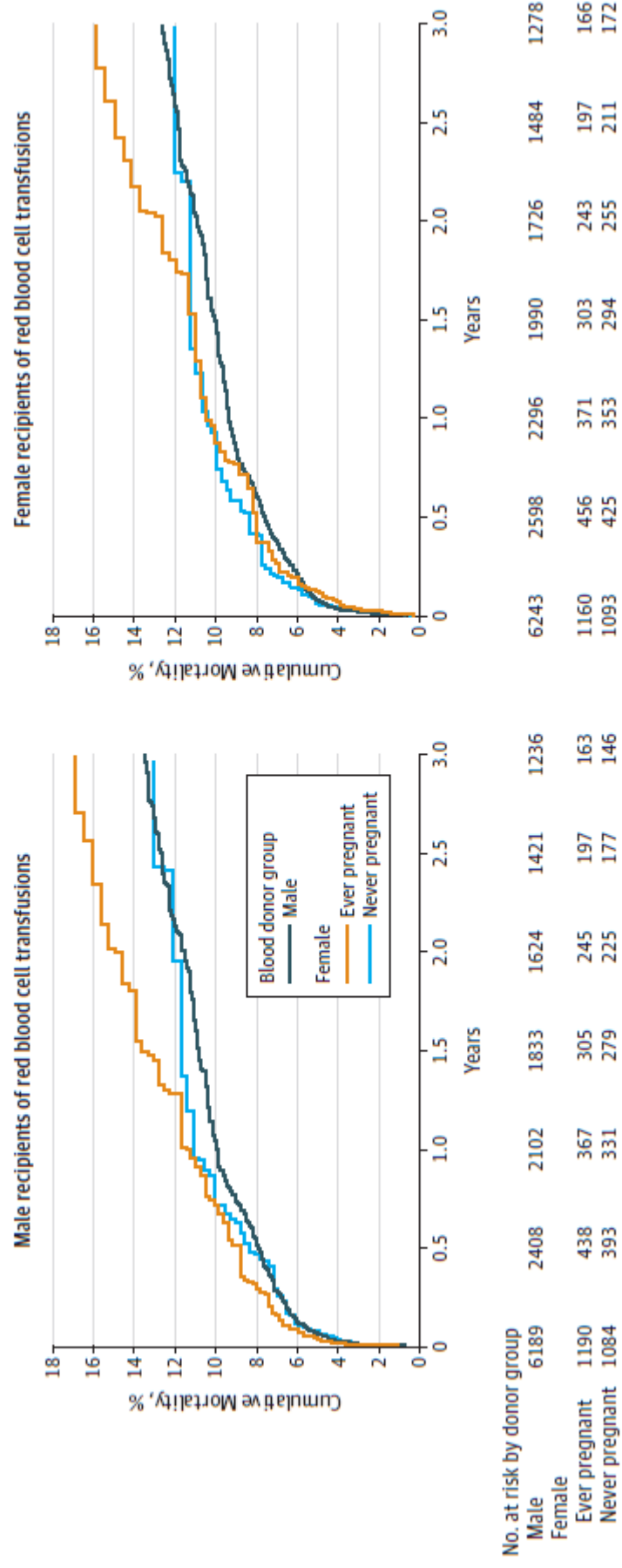
Camila Caram-Deelder, MSc; Aukje L. Kreuger, MD; Dorothea Evers, MD; Karen M. K. de Vooght, PhD;
Daan van de Kerkhof, PhD, MD; Otto Visser, PhD, MD; Nathalie C. V. Péquériau, PhD; Francisca Hudig, PhD, MD;
Jaap Jan Zwaginga, PhD, MD; Johanna G. van der Bom, PhD, MD; Rutger A. Middelburg, PhD

- Méthodologie différente
- Cohorte plus “pure”
 - Et immense

Table 2. Mortality Hazard Ratio of Male and Female Transfusion Recipients Exposed to Red Blood Cell Transfusions From Female (Never-Pregnant or Ever-Pregnant) Donors vs Male Donors in the No-Donor-Mixture, Single-Transfusion, and Full Cohorts^a

Donor Category	Male Recipients		Female Recipients		P Value	HR (95% CI) ^b	P Value
	No. of Deaths Among Recipients/ No. of Recipients	HR (95% CI) ^b	No. of Deaths Among Recipients/ No. of Recipients	HR (95% CI) ^b			
No-Donor-Mixture Cohort^c							
Male	1722/12 212	1 [Reference]	1752/13 332	1 [Reference]			
Ever-pregnant female	1873/13 669	1.13 (1.01-1.26)	1871/14 770	0.99 (0.87-1.13)	.03		.92
Never-pregnant female	1831/13 538	0.93 (0.81-1.06)	1868/14 685	1.01 (0.88-1.15)	.29		.92
Single-Transfusion Cohort^d							
Male	434/6189	1 [Reference]	433/6243	1 [Reference]			
Ever-pregnant female	532/7379	1.23 (0.98-1.54)	517/7403	1.12 (0.88-1.42)	.08		.37
Never-pregnant female	508/7273	0.96 (0.74-1.25)	506/7336	1.00 (0.77-1.30)	.75		.99
Full Cohort^e							
Ever-pregnant analysis							
Male	2538/15 304	1 [Reference]	2448/16 617	1 [Reference]			
Ever-pregnant female	2689/16 338	1.08 (1.02-1.15)	2567/17 654	0.99 (0.93-1.07)	.02		.87
Never-pregnant analysis							
Male	2521/15 163	1 [Reference]	2447/16 608	1 [Reference]			
Never-pregnant female	2630/16 091	1.06 (0.99-1.14)	2563/17 593	0.96 (0.89-1.03)	.08		.23

Figure. Cumulative Incidence of Death According to Sex of the Transfusion Recipient and Sex and Pregnancy History of the Donor in the Single-Transfusion Cohort

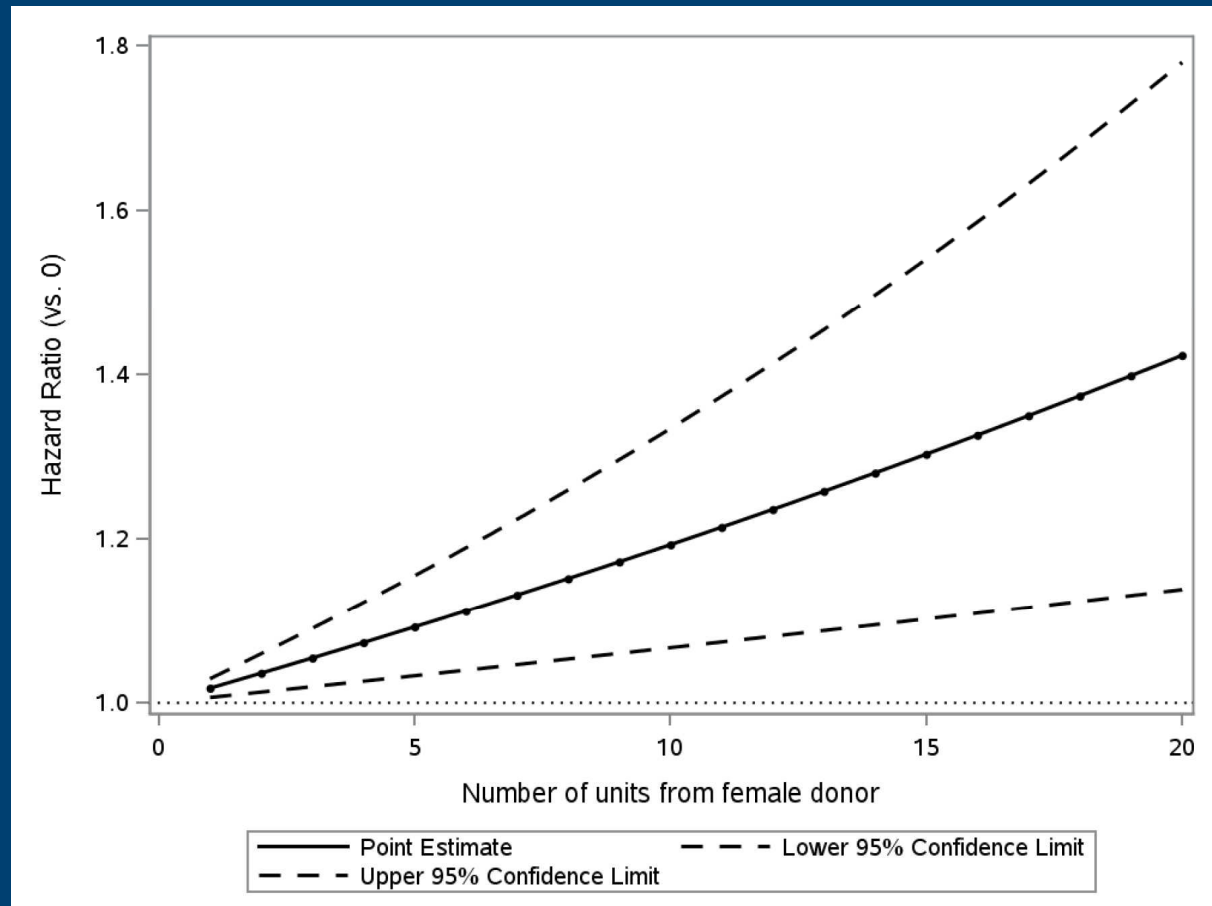


ETABLE 3. SUBGROUP ANALYSES

	Male Recipients			Female recipients			
	HR*	LCI	UCI	HR*	LCI	UCI	
Donor age (years)	17 – 19.9	1.14	1.11	1.17	0.99	0.95	1.03
	20 – 29.9	1.08	1.05	1.11	1.01	0.98	1.05
	30 – 39.9	1.04	1.01	1.07	0.95	0.92	0.99
	40 – 49.9	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	50 – 59.9	1.01	0.99	1.03	0.96	0.93	0.99
60 – 69.9	1.00	0.97	1.02	0.99	0.97	1.02	
≥ 70.0	0.97	0.89	1.07	0.90	0.80	1.01	
Donor sex	Female	1.08	1.07	1.10	1.03	1.02	1.05
	Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

Updated analysis

- Edgrens model:



Prochaines étapes

- Raffiner les analyses
- Autres expositions?
 - Groupe sanguine (en cours) ?
 - Manufacture (en cours) ?
 - Autres infections?
 - Biomarqueurs?
- Autres outcomes
 - Cancer (en cours) ?
 - Infections (en cours) ?
 - IM (en cours) ?
 - Insuf rénale (en cours)
- Autres croisements?
 - Potentiel détudes de mécanismes?

Étude de confirmation



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PROTECTED WHEN
COMPLETED

Appl. #

Application Details

Funding Opportunity:

Project Grant: Fall 2016 (2016-10-20)

Research Proposal

An innovative Trial Assessing Donor Sex on Recipient Mortality (iTADS)

Chassé, Fergusson

- Financée Printemps 2017
- RCT
- 8000 patients
- Sang uniquement homme vs uniquement femme
- PI: Chassé M, Fergusson DA.
- Premiers résultats attendus 2020

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Conclusion

- Les caractéristiques des donneurs pourraient affecter l'issue clinique des receveurs
 - Même à long terme
- L'âge et le sexe des donneurs semblent être d'importance
 - Besoin de confirmation
 - Études en cours

Remerciements



- Scientists
 - Dean Fergusson
 - Jason Acker
 - Alan Tinmouth
 - Lauralyn McIntyre
 - Shane English
 - Alan Forster
 - Carl van Walraven
 - Kumanan Wilson
 - Greg Knoll
 - Tim Ramsay
 - Monica Taljaard
 - Nadine Shehata
 - Steven Hawken
- Research assistant
 - Robin Ducharme
 - Diana Wolfe
 - Pauline Quach
 - Malia Murphy
- Administrative support
 - Jodi Peters
 - Irwin Schweitzer
- The Ottawa Hospital Data Warehouse
 - Deanna Rothwell
 - Jocelyn Tufts
- ICES
 - Meltum Gulsum Tuna
 - Glenys Smith

