Chronic statin use is associated with reduced overall and cancer-specific mortality in patients undergoing radical cystectomy for bladder cancer

Michel Wissing, Ana O'Flaherty, Alice Dragomir, Simon Tanguay, Wassim Kassouf, Armen Aprikian

Michel D. Wissing, MD, PhD
Postdoctoral fellow
Division of Cancer Epidemiology

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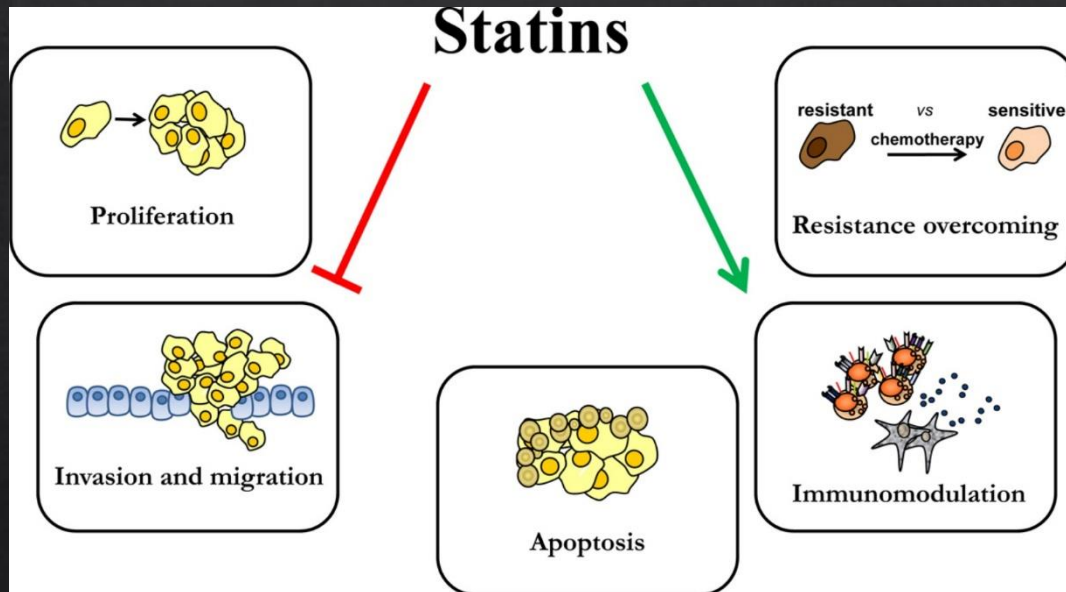# CUA 2019
Potential Conflict of Interest Disclosure

I have no conflict of interest to disclose.

Introduction

Preclinical studies

Clinical studies

- NMIBC:
  - Hoffmann et al, 2006: statin use increases the risk of disease progression
  - Other studies: statins do not change NMIBC outcomes.
- MIBC (RC):
  - Da Silva et al. 2013:

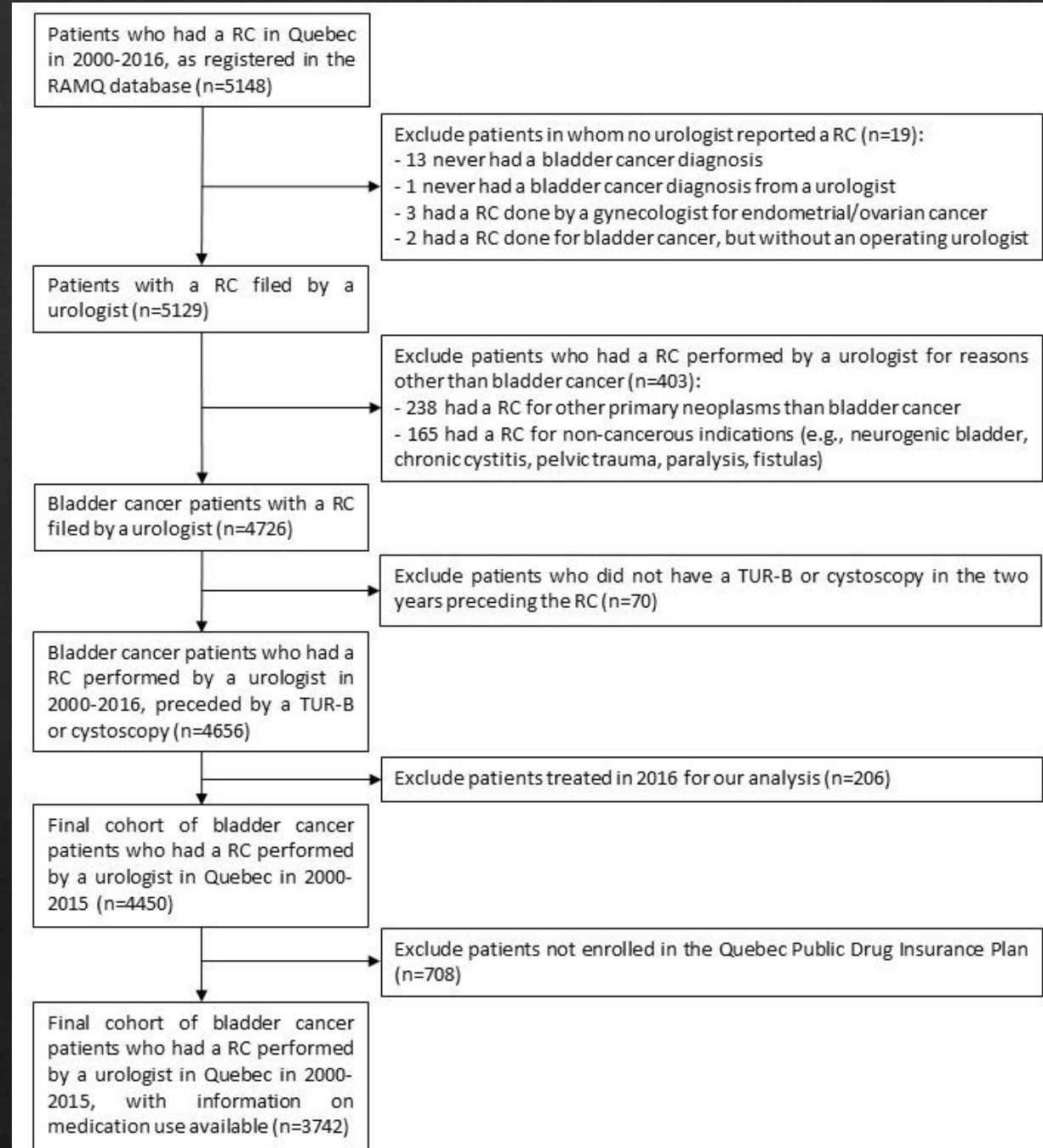|	Disease recurrence	Cancer-specific mortality
Univariable	**1.22 (1.03-1.46)**	**1.26 (1.04-1.54)**
Multivariable	1.04 (0.86-1.24)	1.04 (0.84-1.28)

Pisanti et al., Pharmacol Res 2014, PMID 25009097; Hoffmann, N Engl J Med 2006, PMID 17183004; Hoffmann, N Engl J Med 2006, PMID 17183004; Kamat N Engl J Med 2007, PMID 17377172; Skolarus J Am Coll Surg 2009, PMID 19632602; Crivelli, BJU Int 2013, PMID 23795797; Richard, Urol Oncol 2017, PMID 28190747; Da Silva, J Urology 2013, PMID 23395802

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Research aim

To evaluate whether chronic statin use predicts outcome in a Quebec cohort of bladder cancer patients undergoing radical cystectomy

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Methods (1)

- Quebec provincial health administrative databases: RAMQ, MSSS, ISQ

- All patients who underwent radical cystectomy between 2000 and 2015. Selection of patients: see flow chart.

- Last follow-up: 31 December 2016

Patients who had a RC in Quebec in 2000-2016, as registered in the RAMQ database (n=5148)

Exclude patients in whom no urologist reported a RC (n=19):
- 13 never had a bladder cancer diagnosis
- 1 never had a bladder cancer diagnosis from a urologist
- 3 had a RC done by a gynecologist for endometrial/ovarian cancer
- 2 had a RC done for bladder cancer, but without an operating urologist

Patients with a RC filed by a urologist (n=5129)

Exclude patients who had a RC performed by a urologist for reasons other than bladder cancer (n=403):
- 238 had a RC for other primary neoplasms than bladder cancer
- 165 had a RC for non-cancerous indications (e.g., neurogenic bladder, chronic cystitis, pelvic trauma, paralysis, fistulas)

Bladder cancer patients with a RC filed by a urologist (n=4726)

Exclude patients who did not have a TUR-B or cystoscopy in the two years preceding the RC (n=70)

Bladder cancer patients who had a RC performed by a urologist in 2000-2016, preceded by a TUR-B or cystoscopy (n=4656)

Exclude patients treated in 2016 for our analysis (n=206)

Final cohort of bladder cancer patients who had a RC performed by a urologist in Quebec in 2000-2015 (n=4450)

Exclude patients not enrolled in the Quebec Public Drug Insurance Plan (n=708)

Final cohort of bladder cancer patients who had a RC performed by a urologist in Quebec in 2000-2015, with information on medication use available (n=3742)

Methods (2)

◈ **Chronic statin user:** ≥1 statin prescription before RC and statin prescriptions ≥365 days between the first and last prescription

◈ **Never statin user:** neverpurchased a statin at a Quebec pharmacy in the two years prior to RC until the end of follow-up

◈ **New statin user:** first statin prescription in the year after surgery (controls: never statin users who survived ≥1y postoperatively)

Analyses:

◈ Overall, bladder cancer-specific, and recurrence-free survival

◈ Survival analyses: Kaplan-Meier curves, log-rank tests, Cox proportional hazard models

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Results – cohort characteristics (1)

	never statin users	chronic statin users	P-value
Number of patients	1754	1406	
Age, median (IQR)	70 (62-76)	72 (67-77)	<0.001
Sex			
- Male	1244 (70.9%)	1113 (79.2%)	<0.001
- Female	510 (29.1%)	293 (20.8%)	
Charlson's comorbidity index	6 (5-8)	7 (6-9)	
- Index ≥10	125 (7.1%)	274 (19.5%)	<0.001
- Range	2-18	2-15	
Year of surgery			
- 2000-2009	1138 (64.9%)	632 (45.0%)	<0.001
- 2010-2015	616 (35.1%)	774 (55.0%)	
Hospital type, academic	904 (51.5%)	711 (50.6%)	0.59
Distance to hospital in km, median (IQR)	19.0 (6.9-66.5)	20.6 (7.9-87.5)	0.029
Hospital RC volume per active year, median (IQR)	13.4 (6.6-32.2)	13.8 (8.9-32.2)	0.003
Surgeon RC volume per active year, median (IQR)	6.7 (4.1-13.1)	8.1 (4.7-13.1)	0.005
Neoadjuvant chemotherapy	108 (6.2%)	75 (5.3%)	0.33

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Results – chronic statin use

	Univariable	Multivariable[1]
Overall survival	0.86 (0.79-0.94)	0.83 (0.75-0.91)
Bladder cancer-specific survival	0.79 (0.71-0.88)	0.81 (0.72-0.91)
Recurrence-free survival	0.80 (0.72-0.89)	0.83 (0.74-0.93)

[1]Adjusted for age, sex, Charlson's comorbidity index, year of surgery, type of hospital (academic/non-academic), distance to the hospital, hospital and surgeon's radical cystectomy volume, and neoadjuvant chemotherapy.


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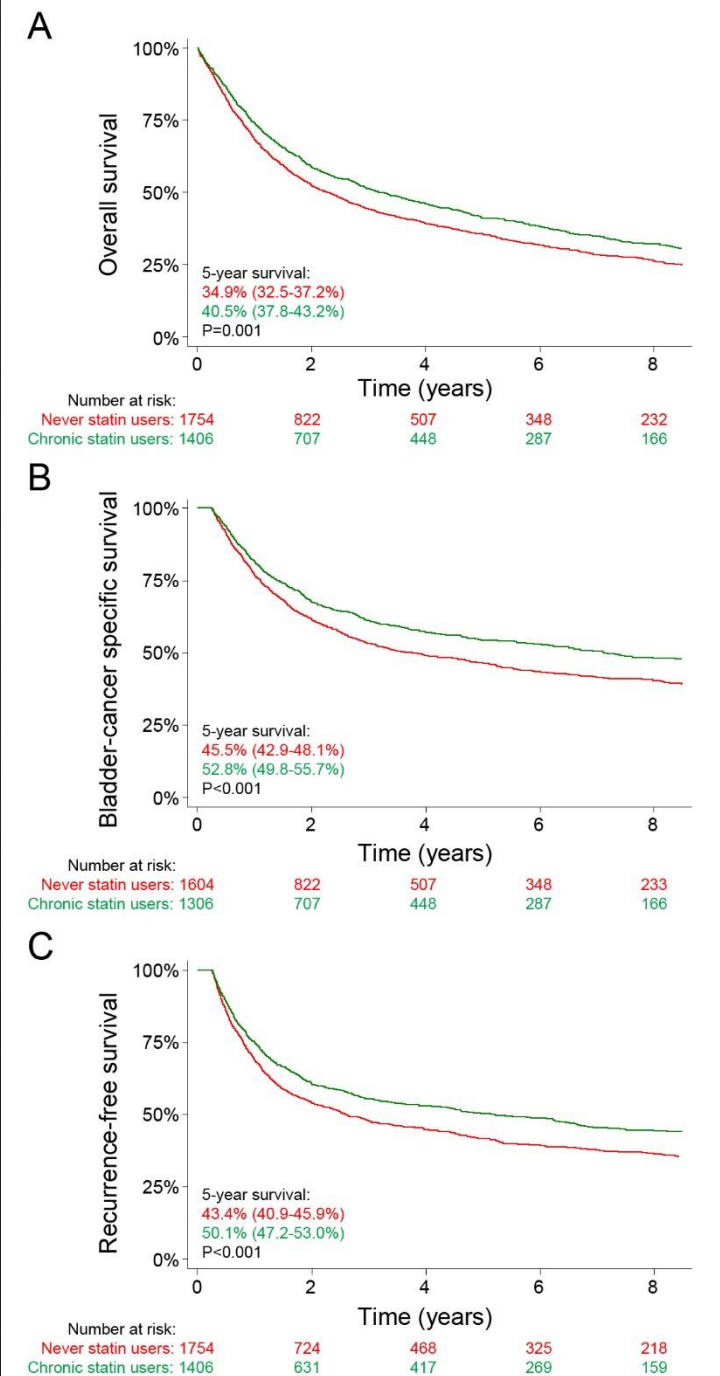
Results – cohort characteristics (2)

	never statin users	new statin users	P-value
Number of patients	1168	91	
Age, median (IQR)	68 (61-75)	66 (64-73)	0.57
Sex			
- Male	825 (70.6%)	75 (82.4%)	**0.016**
- Female	343 (29.4%)	16 (17.6%)	
Charlson's comorbidity index	6 (5-8)	7 (6-9)	
- Index ≥10	91 (7.8%)	10 (11.0%)	**<0.001**
- Range	2-15	2-12	
Year of surgery			
- 2000-2009	756 (64.7%)	50 (54.9%)	0.06
- 2010-2015	412 (35.3%)	41 (45.1%)	
Hospital type, academic	605 (51.8%)	35 (38.5%)	**0.014**
Distance to hospital in km, median (IQR)	18.2 (7.1-63.6)	18.8 (8.0-57.3)	0.94
Hospital RC volume per active year, median (IQR)	13.4 (7.8-32.2)	12.8 (5.3-16.1)	0.052
Surgeon RC volume per active year, median (IQR)	6.7 (4.7-13.1)	6.7 (4.7-13.1)	0.81
Neoadjuvant chemotherapy	75 (6.4%)	4 (4.4%)	0.44

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Results – postoperative statin use

	Univariable	Multivariable[1]
Overall survival	0.92 (0.68-1.24)	0.95 (0.69-1.30)
Bladder cancer-specific survival	0.81 (0.55-1.18)	0.87 (0.59-1.27)
Recurrence-free survival	0.89 (0.63-1.24)	0.95 (0.67-1.33)

[1]Adjusted for age, sex, Charlson's comorbidity index, year of surgery, type of hospital (academic/non-academic), distance to the hospital, hospital and surgeon's radical cystectomy volume, and neoadjuvant chemotherapy.
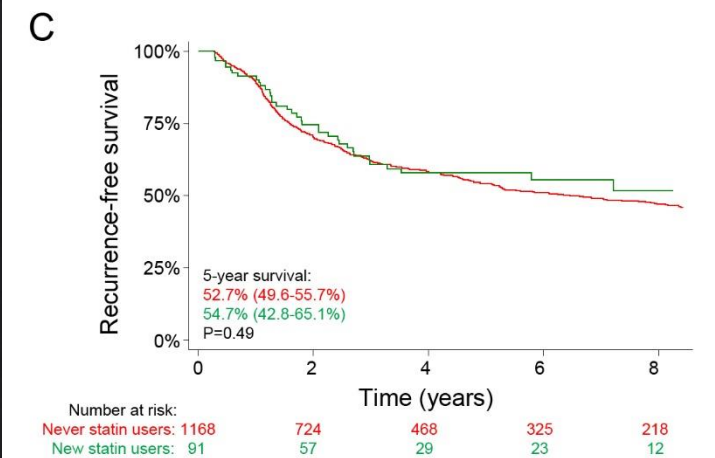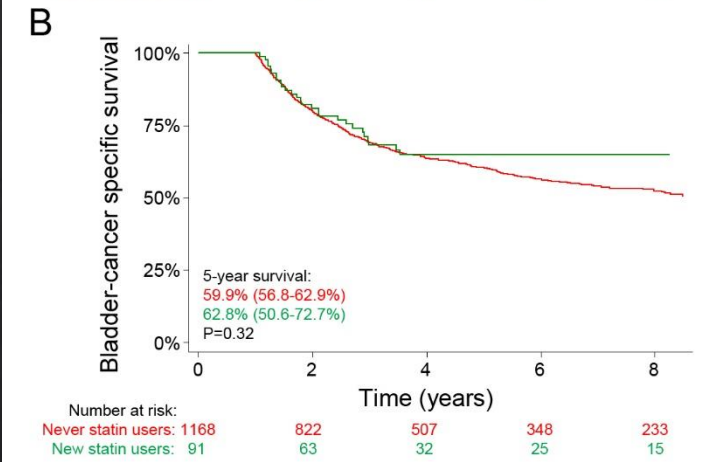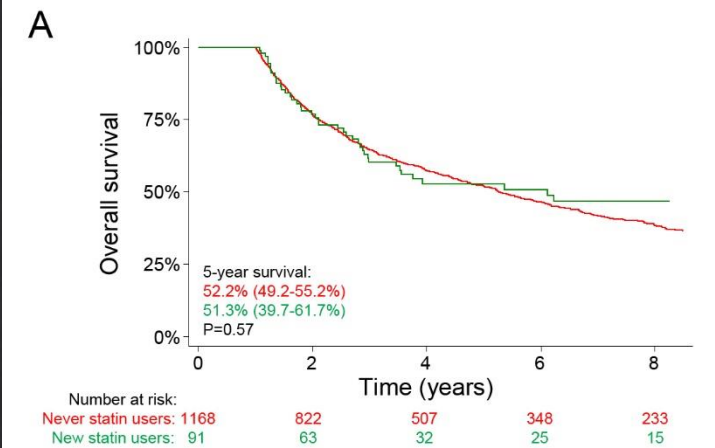
Conclusions

In our cohort of bladder cancer patients undergoing radical cystectomy in Quebec, 2000-2015:

◈ Chronic statin users had a better clinical outcome than never statin users;

◈ Patients who started statin therapy postoperatively did not have improved clinical outcome compared to never statin users.

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Limitations / future perspectives

- Strengths:
  - Large cohort with long follow-up
  - Chronic statin users
  - No immortal time bias
  - Inclusion of all patients in Quebec
- Limitations:
  - **Missing variables:** statin duration/dose, treatment adherence, pathology reports, uncertainty of diagnosis, medical history, smoking status etc.
  - Retrospective study, **selection bias** / healthy user bias
  - Low power for postoperative statin initiation
- Future studies: statin dose, other medications

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