The impact of the Choosing Wisely Canada campaign on the simultaneous use of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin renin blockers (ARB): Interrupted Time Series Analysis.

Authors:

Tracey-Lea Laba, PhD[1*]

Heather C. Worthington, MSc[2]

Lucy Cheng, MSc[2]

Fiona K.I Chan MSc[3]

Nick Bansback, PhD[2]

Michael R. Law, PhD[2]

1 The Centre for Health Economics Research and Evaluation, University of Technology Sydney

2 The University of British Columbia, Centre for Health Services and Policy Research, School of Population and Public Health.

3 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal Canada

*Corresponding Author: tracey.laba@chere.uts.edu.au

Competing interests

Michael Law has consulted for Health Canada, the Hospital Employees' Union, the Conference Board of Canada, and provided expert witness testimony for the Attorney General of Canada. All other authors report no potential conflicts of interest.

1

Abstract

Background

Choosing Wisely (CW) is a high-profile campaign seeking to reduce the use of low-value care. Its impact on low-value pharmaceutical utilization is not well established. We investigated the impact of a recommendation against using combination angiotensin converting enzyme inhibitors and angiotensin receptor blockers for the management of hypertension, heart failure, or diabetic nephropathy.

Methods

We identified all persons continuously registered with British Columbia's Medical Service Plan between 2010 and 2017 with the targeted conditions. Using prescription claims data and an interrupted time series analysis, we estimated per month the number of people on combination therapy, proportion of days covered (PDC), and proportion of all combination prescriptions initiated two years preceding and following the recommendation.

Results

Of 1,104,593 individuals in our study cohort, 4.6% were exposed to combination therapy, largely prescribed by family physicians (84%). The number of people on combination therapy and the PDC were declining prior to the recommendation, but the proportion of combination prescriptions initiated was increasing. Following the recommendation, we observed no statistically significant changes in the level of any outcome. Counter to expectations, the pre-existing downward trend of the monthly number of people decelerated (16.8, 95%CI 14.0, 19.5, P<0.001) and the proportion of prescriptions initiated increased (0.13%, 95%CI: 0.08,0.18, P<0.001).

Conclusions

The CW recommendation was not associated with reduced combination therapy use in the targeted conditions. The observed pre-existing declines in this practice questions the process of selecting recommendations, and the optimal implementation and value of CW without other reinforcing interventions.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2

Introduction

Choosing Wisely™ (CW) is an international campaign seeking to reduce waste in health systems by reducing the use of low-value care, namely medical treatments, services, and procedures offering no or little benefit.[1] Originating as a joint venture between the American Board of Internal Medicine and Consumer Reports, the initial CW mandate generated a list of physician-identified low-value practices that were communicated via mass media to "spark" conversations between patients and providers.[2] The CW campaign has diffused widely, with presence in more than 20 countries.[3] In Canada, over 300 recommendations have been released since 2014 with almost 70 clinician societies participating in their development.[4]

Alongside its expansion, the methods employed by CW have been subject to criticism. Critics consider CW a "re-branding of common sense"[5] and highlight the non-transparent and non-standardised derivation of lists and targeting of obsolete rather than low-value, high volume practices.[6] Early evaluation of CW provides some support for this view, with several recommendations showing no impact on reducing low-value care when assessed in large, national US datasets.[7]

Specifically, regarding low-value pharmaceutical use, there are few evaluations despite several targeted CW recommendations. In Rosenberg's analyses of nationwide commercial health plan population-level data, non-steroidal anti-inflammatory drug (NSAID) use in people with heart failure, hypertension and chronic kidney disease paradoxically increased, while the use of antibiotics for acute sinusitis did not change.[7] In another US study,[8] the overuse of expensive antiemetics for chemotherapy-induced nausea and vomiting initially decreased, but this trend reversed six months after the CW recommendation. Overall, this evidence remains equivocal on whether CW influences prescribing.

We sought to fill this evidence gap by examining the extent of use of a low-value pharmaceutical practice and the impact of a CW recommendation on this use. In our study, we evaluate the extent and changes in population-level use of combination angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (herein combination therapy) for the treatment of hypertension, diabetic nephropathy or heart failure in British Columbia, Canada. This recommendation was proposed by the Canadian nephrology association in 2014 based on rigorous clinical evidence[9] and is supported by the 2014 Eighth Joint National Committee (JNC 8)[10] and the 2014 Canadian Hypertension Education program guidelines.[11] Given the strength of evidence supporting this recommendation, and the lack of uncertainty in its clinical application, we hypothesised that if CW was effective, this is an instance where a change in prescribing should have been observable.

3

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

Study Context

The Canadian CW campaign has engaged more than 90% of all national medical specialty societies and is endorsed by all the Canadian provincial and territorial medical associations.[12] Each medical specialty develops specialty-relevant, evidence-based lists recommending unnecessary tests and treatments to avoid. These recommendations are available to physicians (e.g. through a mobile app and on the campaign's website) and to patients (e.g. via posters displayed in general practice surgeries). Implementation of each recommendation is context-specific. Several provincial and territorial-specific campaigns have also been developed to prioritise and accelerate the adoption of regionally-relevant recommendations from the national campaign.[13]

Data sources

We used six population-based data systems on health services utilization in the province between 2010 and 2017. We obtained fee-for-service physician consultation and expenditure information through the Medical Services Plan billings data,[15] and hospital admission information from the Discharge Abstract Database.[16] We used the BC PharmaNet database,[17] which is a complete record of all drug dispensations in British Columbia, to track drug utilisation and expenditure. We obtained demographic information about the population from the MSP registry file[18] and Vital Statistics Mortality data,[19] and prescriber speciality information from the College of Physicians and Surgeons of British Columbia,[20] which was linked via a unique practitioner identifier. These datasets were linked using a unique patient health number by Population Data BC.

Study population

We included all individuals diagnosed with hypertension, heart failure or diabetic nephropathy using International Classification of Diseases (ICD)-9 and -10 codes previously used in the literature for these conditions (ICD-9: 401; 402; 403; 404; 405; 250.4*; 428; 250 AND (580 OR 581 OR 582 OR 583 OR 585 OR 586 OR 592 OR 593.3 OR 584; ICD-10: I10; I11; I12; I13; I15; E10.2*; E11.2*; E13.2*; I50, E10-14 AND (N00-N23)).[21, 22] People with one code recorded in the DAD or two of the same codes recorded in the MSP within 2 years were included. For diabetic nephropathy, we included all people with diabetes and any kidney related complication. People who ceased enrolment in MSP for reasons other than death were excluded. In addition, people who were in receipt of drug benefits through the Federal government (e.g. First Nations, military) were excluded because information about their drug utilisation and expenditure was not captured in PharmaNet.

Outcomes - Combination therapy use

We measured the number of people on combination therapy, the mean proportion of days covered (PDC) for combination therapy and the proportion of combination therapy prescriptions initiated per month. To determine combination treatment, we identified all prescriptions containing an ACEI or ARB using the Anatomical Therapeutic Classification codes C09A-D.[23] For each individual, we created a matrix which indicated each ARB-containing medication used. A variable was created to indicate in each month when combination therapy was initiated and/or stopped, with a gap in treatment of combination therapy of more than 90 days indicating treatment cessation. For each combination therapy, the specialty of the physician (nephrologist, family physician or other) prescribing the second agent in the combination was recorded.

To calculate the proportion of days covered (PDC) for combination treatment, we first determined the PDC for any ACEI- or ARB-containing medicine and then determined the PDC when *both* ACEI-

4

and ARB-containing medicines were available per month in the overall cohort. The PDC is a ratio between 0 and 1 of the number of days in a period when a medication is available divided by the number of days in the period.[24] The PDC is endorsed by the National Quality Forum for measuring health care quality.[25] A decrease in PDC represents reduced medication use. We express PDC as a percentage and inferred reduced PDC as reduced exposure and therefore combination therapy use.

Statistical analysis

We used an interrupted time series (ITS) analysis[26] to determine the impact of the CW recommendation on outcomes. ITS is used increasingly in health services research[27-29] because, unlike most other observational research designs, pre-existing secular trends in outcomes are controlled for so that causal effects of an intervention can be estimated.[26] In our analyses, we estimated the change in the immediate level and the trend of each outcome 24 months before and after the release of the CW recommendation against the use of combination therapy in BC (November 2014).

Our analysis was weighted by population size to adequately account for deaths in our cohort, and proximity of time to implementation of the CW recommendation. This was done by creating the time elapsed, centered on implementation, with the biggest weight given to the first implementation observation, and more weight given to time points that were closer to the implementation date. The final weight combined the population size weight and the proximity time weight. We used the generalized least-squares regression and included appropriate factors to account for the autocorrelation in the residuals (i.e autoregressive process of order 1).

As the CW recommendation was endorsed by the Canadian Society of Nephrology, we performed a secondary stratified analysis by the speciality of the physician (nephrology, family physician, other) prescribing the second agent in the combination. We also performed stratified analysis by age ($\leq$65, >65 years) and sex.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

Population characteristics

Our population included 1,104,593 individuals with a diagnosis of hypertension, heart failure or diabetic nephropathy. Our sample was 50.1% female and 51.3% were age 65 years or above (see Table 1) at the time of the CW recommendation. Most people in our sample had a diagnosis of hypertension, pre-dominantly essential hypertension, compared to only 14% with heart failure.

Proportion of combination use

Just under 5% of our population received combination therapy before and after the CW recommendation. While the demographic characteristics of people on combination therapy were similar to the overall population, we noted lower proportions of people with diabetic nephropathy and younger people on combination therapy. Most of the combination therapy in our sample was prescribed by family physicians (84%), as opposed to nephrologists (4%) or other specialists (13%).

Number of people per month on combination treatment

Figure 1a displays the ITS results for the number of people per month on combination treatment. Prior to the CW recommendation, the number of people on combination treatment per month was declining (-27.5 95%CI -29.5, -25.5, P<0.001). Following the CW recommendation, we did not see a statistically significant change in the level (18.5 95%CI -21.9 58.8, P=0.37). Counter to expectations, we found an attenuation of the pre-existing declining trend of number of people on combination treatment per month, with a statistically significant increase of 16.8 people per month (95%CI 14.0, 19.5, P<0.001).

When stratified by prescriber specialty (see Figure 1b), we saw similar trends however the attenuation of the pre-existing declining trend was not statistically significant for physicians who were not family physicians or nephrologists (-0.3 95%CI -1.5, 0.9, P=0.6).

Exposure to combination therapy: Mean proportion of days covered for combination therapy

Figure 2a displays the ITS results for mean PDC for combination treatment per month. In the two years prior to the CW recommendation mean PDC was decreasing (-0.26% 95%CI -0.29, -0.22 P<0.001). Following the CW recommendation, we did not see a statistically significant change in the level (0.63% 95%CI -0.05, 1.32, P=0.08). but a small yet statistically significant acceleration of the pre-existing trend by 0.10% per month (95%CI -0.15, -0.06, P<0.001).

When stratified by prescriber specialty, we saw similar trends (see Figure 2b) however the change in the pre-existing trend was only statistically significant for family physicians (0.09% 95%CI0.15, -0.04 P<0.01).

Proportion of combination therapy prescriptions that were initiated per month

Figure 3a displays the ITS results for the proportion of all combination therapy prescriptions that were initiated per month. Prior to the CW recommendation, the proportion of combination treatment prescriptions initiated was increasing by 0.26% per month (95%CI 0.22, 0.30, P<0.001). Following the CW recommendation, we saw a trend towards a reduction in the immediate level that was not statistically significant (-0.69% 95%CI -1.38, 0.01, P=0.06), and, counter to expectations, we saw a statistically significant increase in the pre-existing trend (0.13% 95%CI 0.08 0.18, P<0.001).

We saw similar results when this outcome was stratified by prescriber specialty (see Figure 3b), with the trend towards a statistically significant reduction in the immediate level only evident with

6

nephrologists (-1.4% 95%CI -3.03, 0.17, P=0.09) and the increase in the pre-existing trend not statistically significant for physicians who were not family physicians or nephrologists (0.08% 95%CI -0.19, 0.34, P=0.58).

Stratified analyses by sex and age ($\geq$65 versus <65) were also examined, but did not reveal any differences except for a statistically significant increase in the level of mean PDC for females immediately after the CW recommendation (1.56% 95%CI 0.72, 2.39, P<0.001) (not shown, available upon request).

7

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTERPRETATION

This is the first study to evaluate the impact of the CW recommendation seeking to reduce combination ACEI and ARB use for the treatment of hypertension, heart failure and diabetic nephropathy. Despite this recommendation being supported by strong clinical evidence with clear clinical application,[9, 11] in this rigorous population-level analysis, we did not find equivocal evidence to support the effectiveness of CW on reducing this low value pharmaceutical practice. While we saw a small improvement in the already declining rate of exposure to combination therapy after the CW recommendation, counter to expectations, we found the number of people on combination therapy increased in the two-year period after the CW recommendation along with the proportion of combination prescriptions initiated.

Our study reinforces findings from the small body of evidence that demonstrates little to no impact of CW recommendations alone on the use of low value pharmaceuticals.[7, 8] Using more rigorous analytical methods that can account for secular trends and pre-existing patterns of use, we found that CW had no immediate impact on the use of this infrequently used low-value pharmaceutical practice and attenuated some of the reductions already occurring over time. We also found that the extent of combination therapy was comparable to other provinces[30] but represented less than 5% of our population, and that most prescribing was performed by family physicians, rather than the society endorsing the recommendation. These findings reinforce previous concerns raised about selecting "easy target" low-value practices[5, 6, 31] - i.e. practices performed by other specialities, infrequently or that are obsolete - and supports calls to improve methods to identify high-priority clinical targets to fulfil the promise of the CW campaign.[32]

It could be argued that the lack of measurable impact of CW is because additional interventions are needed to permit wider and more sustained implementation.[2, 32] This may be particularly relevant in BC where the CW campaign has received less investment than other Canadian provinces, albeit anecdotally.[12] However, the inability of CW to change physician behaviour is not surprising given the large body of evidence prior to CW questioning the impact of passive, generalised, physician-targeted information-provision campaigns to change physician behaviour, including prescribing practice.[33-36] Behavioural "nudge" approaches and other theory-based interventions have since been suggested to improve the implementation of CW.[32, 37] But considering the large investments already made in the CW campaign, the incremental costs and benefits of a modified CW approach compared to its current format should be further evaluated, as well as the economic viability of the CW approach as compared to other strategies to lower low-value prescribing.

Limitations

As CW was implemented nationally at a fixed date, there was not an appropriate control group that could be used in our analysis. Further, we did not have the exact clinical context and there may be individuals where combination therapy may be appropriate. However, we expect this would have been a very small proportion of our population[38] and would not have changed as a result of CW. It is also possible that interventions to reduce combination therapy prescribing (e.g. physician detailing) were implemented at the same time as the CW campaign which we are not privy to and which could impact our effect estimates. However, as the pivotal evidence for this recommendation and associated updates to clinical guidelines occurred many years before the CW recommendation, we expect the likelihood of this as low. It is unclear if the CW campaign was as active in BC as other provinces, so these results may not fully extrapolate to other settings.

8

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusions

The release of the CW recommendation alone did not reduce the concomitant use of ACEI and ARB for the management of hypertension, heart failure, or diabetic nephropathy in British Columbia. Our findings reinforce the limited effectiveness of passive, information provision strategies to improve medicine use. Future consideration of coupling CW with other established behaviour-change interventions with rigorous evaluation of its effects is suggested. The observed pre-existing declines in the use of this low value practice also calls into question the process of selecting recommendations.

9

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1.   Born KB, Levinson W. Choosing Wisely campaigns globally: A shared approach to tackling the problem of overuse in healthcare. J Gen Fam Med. 2019;20(1):9-12.

2.   Levinson W, Born K, Wolfson D. Choosing Wisely Campaigns: A Work in Progress. JAMA. 2018;319(19):1975-6.

3.   Choosing Wisely Canada. Choosing Wisely International Campaigns: Choosing Wisely Canada; 2019 [Available from: https://choosingwiselycanada.org/campaign/international/.

4.   Canada CW. Recommendations and Resources 2019 [Available from: https://choosingwiselycanada.org/recommendations/.

5.   Atkinson P, Lang E, Mackenzie M, Hirandani R, Lys R, Laupacis M, et al. CJEM Debate Series: #ChoosingWisely - The Choosing Wisely campaign will not impact physician behaviour and choices. CJEM. 2018;20(2):170-5.

6.   Morden NE, Colla CH, Sequist TD, Rosenthal MB. Choosing wisely--the politics and economics of labeling low-value services. N Engl J Med. 2014;370(7):589-92.

7.   Rosenberg A, Agiro A, Gottlieb M, Barron J, Brady P, Liu Y, et al. Early Trends Among Seven Recommendations From the Choosing Wisely Campaign. JAMA Intern Med. 2015;175(12):1913-20.

8.   Encinosa W, Davidoff AJ. Changes in Antiemetic Overuse in Response to Choosing Wisely Recommendations. JAMA Oncol. 2017;3(3):320-6.

9.   Chan E, Hemmelgarn B, Klarenbach S, Manns B, Mustafa R, Nesrallah G, et al. Choosing Wisely: The Canadian Society of Nephrology's List of 5 Items Physicians and Patients Should Question. Can J Kidney Health Dis. 2017;4:2054358117695570.

10.   James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.

11.   Dasgupta K, Quinn RR, Zarnke KB, Rabi DM, Ravani P, Daskalopoulou SS, et al. The 2014 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Canadian Journal of Cardiology. 2014;30(5):485-501.

12.   Choosing Wisely Canada. Building a movement: the first five years Canada2019 [Available from: https://choosingwiselycanada.org/perspective/cwc-five-years/.

13.   Canadian Institute for Health Information. Unnecessary care in Canada. Ottawa, Canada: CIHI; 2017.

14.   BC Ministry of Health Pharmaceutical Services Division. Understanding PharmaCare plans Victoria2018 [Available from: https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/7-2.pdf.

15.   BC Ministry of Health (2018). Medical Services Plan (MSP) payment information file. Population Data BC. Data Extract. MOH 2018. www.popdata. bc.ca/data..

16.   Canadian Institute for Health Information (2018): Discharge Abstract Database (Hospital Separations). Population Data BC. Data Extract. MOH (2018).http://www.popdata.bc.ca/data.

17.   BC Ministry of Health (2018). PharmaNet. BC Ministry of Health. Data extract. Data Stewardship Committee 2018. www.popdata.bc.ca/data.

18.   British Columbia Ministry of Health (2018): Consolidation File (MSP Registration & Premium Billing). Population Data BC. Data Extract. MOH (2018). http://www.popdata.bc.ca/data.

19.   BC Vital Statistics Agency (2018): Vital Statistics Deaths. Population Data BC. Data Extract BC Vital Statistics Agency (2018). http://www.popdata.bc.ca/data.

20.   BC Ministry of Health (2018): British Columbia College of Physicians and Surgeons. BC Ministry of Health. Data Extract. Data Stewardship Committee (2018). http://www.popdata.bc.ca/data.

10

21.   Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak. 2015;15:31.

22.   Young BA, Pugh JA, Maynard C, Reiber G. Diabetes and renal disease in veterans. Diabetes Care. 2004;27 Suppl 2:B45-9.

23.   ATC/DDD Index 2018 [Internet]. Norwegian Institute of Public Health. 2018.

24.   Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Med Care. 2013;51(8 Suppl 3):S11-S21.

25.   Pharmacy Quality Alliance. Adherence. PQA Measures Alexandria, VA, USA2018 [updated August 28, 2018. Available from: https://www.pqaalliance.org/adherence-measures.

26.   Shadish WR, T.D C, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston: Houghton Mifflin; 2002.

27.   Jandoc R, Burden AM, Mamdani M, Levesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol. 2015;68(8):950-6.

28.   Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr. 2013;13(6 Suppl):S38-44.

29.   Taljaard M, McKenzie JE, Ramsay CR, Grimshaw JM. The use of segmented regression in analysing interrupted time series studies: an example in pre-hospital ambulance care. Implement Sci. 2014;9:77.

30.   McAlister, F. A., Zhang, J., Tonelli, M., Klarenbach, S., Manns, B. J., Hemmelgarn, B. R., & Alberta Kidney Disease Network. The safety of combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers in elderly patients: a population-based longitudinal analysis. CMAJ. 2011;183(6), 655–662.

31.   Grady D, Redberg RF, Mallon WK. How should top-five lists be developed?: what is the next step? JAMA Intern Med. 2014;174(4):498-9.

32.   Kerr EA, Kullgren JT, Saini SD. Choosing Wisely: How To Fulfill The Promise In The Next 5 Years. Health Aff (Millwood). 2017;36(11):2012-8.

33.   Anderson GM, Lexchin J. Strategies for improving prescribing practice. CMAJ. 1996;154(7):1013-7.

34.   Grimshaw JM, Shirran L, Thomas R, Mowatt G, Fraser C, Bero L, et al. Changing provider behavior: an overview of systematic reviews of interventions. Med Care. 2001;39(8 Suppl 2):II2-45.

35.   Majumdar SR, Soumerai SB. Why most interventions to improve physician prescribing do not seem to work. CMAJ. 2003;169(1):30-1.

36.   Soumerai SB, McLaughlin TJ, Avorn J. Improving Drug Prescribing in Primary Care: A Critical Analysis of the Experimental Literature. Milbank Q. 2005;83(4):10.1111/j.468-0009.2005.00435.x.

37.   Mafi JN, Parchman M. Low-value care: an intractable global problem with no quick fix. BMJ Quality & Safety. 2018;27(5):333-6.

38.   Makani Harikrishna, Bangalore Sripal, Desouza Kavit A, Shah Arpit, Messerli Franz H. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials BMJ 2013; 346 :f360

11

Tables

Table 1: Characteristics of population with a diagnosis of hypertension, diabetic nephropathy or heart failure, overall and when dispensed combination angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Characteristic		Overall	Dispensed combination ACEI & ARB
n		**1,104,593**	**51,327**
Age			
	65 years or more	566.755 (51.3%)	29,489 (57.5%)
	Less than 65 years	537,838 (48.7%)	21,838 (42.6%)
Sex (n, %)			
	Female	553,882 (50.1%)	26,971 (52.6%)
	Male	550,387 (49.8%)	24,345 (47.4%)
	Unknown	324 (0.03%)	11 (0.02%)
Hypertension			
	Any	856,705 (84.0%)	47,660 (92.9%)
	Essential Hypertension	853,491 (84.5%)	47,556 (92.7%)
	Hypertensive heart disease	5,765 (0.6%)	451 (0.9%)
	Hypertensive kidney disease	5,568 (0.6%)	595 (1.2%)
	Hypertensive heart and kidney disease	1,013 (0.1%)	104 (0.2%)
	Secondary hypertension	1,256 (0.12%)	98 (0.2%)
Heart Failure			
		143,104 (14.2%)	9,739 (19.0%)
Diabetic Nephropathy			
		556,545 (55.1%)	26,062 (50.8%)

12

FIGURES

Figure 1a: Interrupted time series analysis of the number of people on combination ACEI & ARB 24 months before and after the CW recommendation.

The number of people on combination therapy was declining in the 24 months prior to the CW recommendation (-27.51 95%CI -29.47, -25.54, P<0.001). Following the CW recommendation, there was no significant immediate change in the level (18.46 95%CI -21.86, 58.79, P=0.37) however there was a statistically significant attenuation of the pre-existing declining trend (16.76 95%CI 13.98, 19.54, P<0.001).

13
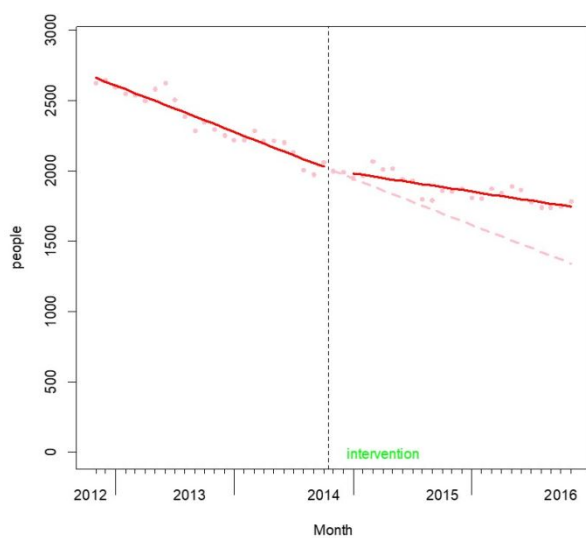
Figure 1b Interrupted time series analysis for the number of people on combination ACEI & ARB per month for i) nephrologists ii) family physicians iii) other specialties

The number of people on combination therapy was declining in the 24 months prior to the CW recommendation for all specialties (i) nephrology: --1.97 95%CI -2.31, -1.62, P<0.001; ii) family physician: -24.07 95%CI –27.03, -21.10, P<0.001; iii) other -0.93 95%CI -1.77, -0.09, P<0.05. Following the CW recommendation, there was no significant change in the levels. However, there was a statistically significant attenuation of the pre-existing declining trend for nephrologists (0.63 95%CI 0.11, 1.15, P<0.05) and family physicians (14.95, 95%CI 10.71,19.20, P<0.001) but not for other specialities (-0.30 95%CI -1.53, 0.94, P=0.64).
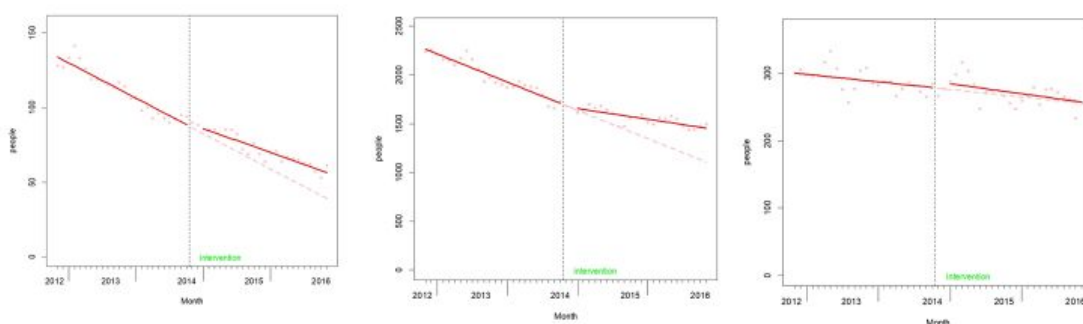

14

Figure 2a: Interrupted time series results for the mean proportion of days covered (PDC, %) for combination ACEI & ARB therapy per month 24 months before and after the CW recommendation

The mean PDC for combination therapy was statistically significantly declining over the 24 months prior to the CW recommendation (-0.26% 95%CI -0.29 to -0.23, P<0.001). Following the CW recommendation there was no statistically significant immediate change in the level (0.63% 95%CI – 0.05, 1.32, P=0.08), however there was a small but statistically significant increase in the pre-existing trend in the 24 months following the CW recommendation (-0.10% 95%CI -0.15 to -0.06, P<0.001).
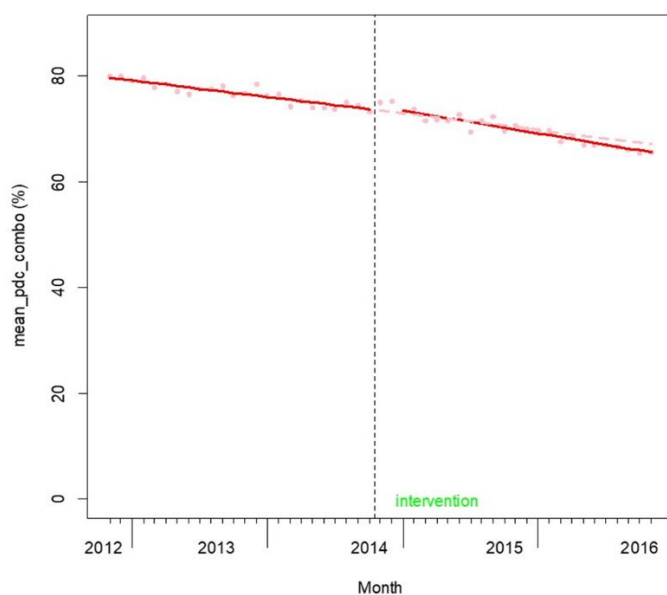

15

Figure 2b: Interrupted time series analysis for the mean proportion of days covered (PDC, %) for combination ACEI & ARB per month for i) nephrologists ii) family physicians iii) other specialties

The mean PDC for combination therapy was declining in the 24 months prior to the CW recommendation for all specialties (i) nephrology: --0.25% 95%CI -0.41, -0.10, P<0.01; ii) family physician: -0.25% 95%CI –0.29, -0.21, P<0.001; iii) other -0.30% 95%CI -0.40, -0.19, P<0.001. Following the CW recommendation, there was no significant change in the levels. However, there was a statistically significant increase in the pre-existing declining trend for family physicians (-0.09%, 95%CI -0.15, -0.04 P<0.01) but not for nephrologists (-0.08% 95%CI -0.31, 0.15, P=0.52) or other specialities (-0.04% 95%CI -0.19, 0.11, P=0.60).

16
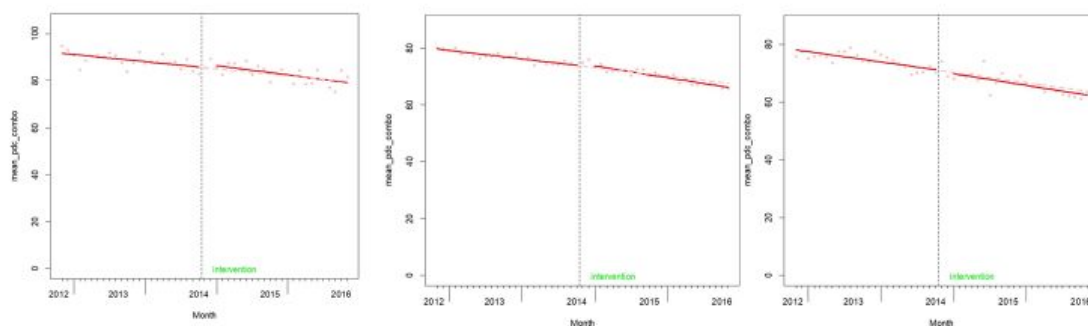
Figure 3a: Interrupted time series results for the proportion of all combination ACEI & ARB prescriptions initiated per month 24 months before and after the CW recommendation

The proportion of all combination therapy prescriptions that were initiated was statistically significantly increasing over the 24 months prior to the CW recommendation (0.26% 95%CI 0.22,0.30, P<0.001). Following the CW recommendation there was no statistically significant immediate change in the level (-0.69% 95%CI −1.38, 0.01, P=0.06), however there was a statistically significant increase in the pre-existing trend in the 24 months following the CW recommendation (0.13% 95%CI 0.08, 0.18, P<0.001).
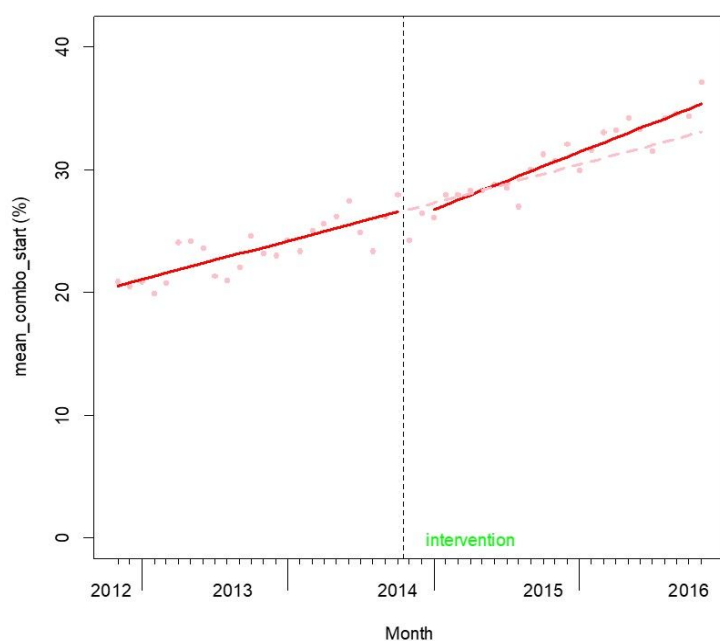

17

Figure 3b Interrupted time series analysis for the proportion of combination ACEI & ARB prescriptions initiated per month for i) nephrologists ii) family physicians iii) other specialties

The proportion of all combination ACEI & ARB prescriptions that were initiated per month was statistically significantly increasing in the 24 months prior to the CW recommendation for all specialties (i) nephrology: 0.15% (95%CI 0.07, 0.24 P<0.001) ; ii) family physician: 0.24% 95%CI 0.20, 0.29, P<0.001; iii) other: 0.29% 95%CI 0.11, 0.47, P<0.01). Following the CW recommendation, there was no significant immediate change in the levels, however there was a statistically significant increase in the pre-existing trend for family physicians and nephrologists, but not for other specialities -(0.08% 95%CI -0.19, 0.34, P=0.58).

18