

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Effect of free distribution of medicines on the process of care for adult patients with type 1 and type 2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042046
Article Type:	Original research
Date Submitted by the Author:	23-Jun-2020
Complete List of Authors:	Charles, Onella; University of Toronto Faculty of Medicine; St Michael's Hospital Centre for Urban Health Solutions Woods, Hannah; St Michael's Hospital Centre for Urban Health Solutions Ally, Muhamad; St Michael's Hospital Centre for Urban Health Solutions Manns, Braden; University of Calgary Cumming School of Medicine, Department of Community Health Sciences ; University of Calgary Cumming School of Medicine, Department of Medicine Shah, Baiju; University of Toronto Institute of Health Policy Management and Evaluation; Institute for Clinical Evaluative Sciences Persaud, Nav; St. Michael's Hospital, Li Ka Shing Knowledge Institute
Keywords:	DIABETES & ENDOCRINOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effect of free distribution of medicines on the process of care for adult patients with type 1 and type 2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings

Onella Charles BSc^{1,2}, Hannah M Woods MSc², Muhamad Z Ally BSc², Braden Manns MD^{5, 6, 7, 8}, Baiju Shah MD^{9,10}, Nav Persaud MD^{2,3,4,9}.

¹ Faculty of Medicine, University of Toronto, 1 King's College Cir, Toronto, ON, Canada

² MAP Centre for Urban Health Solutions, St. Michael's Hospital, 30 Bond St, Toronto, ON, Canada

³ Department of Family and Community Medicine, University of Toronto, 500 University Ave, Toronto, ON, Canada

⁴ Department of Family and Community Medicine, St. Michael's Hospital, 80 Bond st, Toronto, ON, Canada

⁵ Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁶ Department of Medicine, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁷ O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, 3280 Hospital Dr NW, Calgary, AB, Canada

⁸ Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁹ Institute of Health Policy, Management, and Evaluation, University of Toronto, 155 College St, Toronto, ON, Canada

¹⁰ Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Toronto, ON, Canada

Corresponding author: Nav Persaud, 80 Bond St. Toronto, Ontario, Canada M5B 1X2
Nav.persaud@utoronto.ca 416-864-6060 Ext 775778

Key Words: Essential medicine; diabetes; process of care; health outcome

Wordcount: 2802 **Figures:** 1 **Tables:** 3

ABSTRACT

Objectives

The Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial randomized controlled trial showed that patients receiving free access to medicines had improved diabetes and hypertension outcomes compared to patients who had usual access to medicines. In this study, we aimed to test the impact of providing free access to medicine to people with diabetes and hypertension on process of care indicators.

Design

In this post hoc analysis of randomized controlled trial findings we identified process of care indicators for the management of diabetes and hypertension using relevant guidelines. The follow process of care indicators were identified for diabetes management: encounters with healthcare professionals, blood pressure measurements, self-monitoring of blood glucose, annual eye and foot exam, annual administration of the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and urine albumin to creatinine ratio (ACR). We identified the following process of care indicators for hypertension: encounters with healthcare professionals, blood pressure measurements, self-measuring of blood pressure, and serum tests for electrolytes, HbA1c, lipids, and creatinine. Chart extractions were performed for all patients and the indicators for diabetes and hypertension were recorded. We compared the indicators for patients in each arm of the trial.

Results

The study included 268 primary care patients. Free distribution of medicines may improve self-monitoring behaviours (aRR 1.3; 95 % CI 0.7-2.6) and reduce missed primary care appointments for patients with diabetes (aRR 0.8; 95 % CI 0.5-1.3) or hypertension (aRR 0.4; 95 % CI 0.2-0.9). Free distribution may also reduce primary care and consultant appointments and laboratory testing in patients with hypertension.

Conclusions

1
2
3 Improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate
4 health outcomes but also improves the patient experience and may also reduce healthcare costs by
5 encouraging self-monitoring.
6
7
8
9

10 11 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 12 • The study is based on a randomized controlled trial.
- 13 • Despite the fact that this was a post-hoc analysis and randomization was not stratified based on
14 these characteristics, we found that the groups were largely balanced.
- 15 • Associations identified during post-hoc analyses could be spurious and thus the findings should
16 be viewed as hypothesis-generating.
- 17 • The trial this study was based on was conducted with primary care patients in a high-income
18 country who reported cost-related non-adherence and the findings may not apply in other settings.
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

INTRODUCTION

Managing people with chronic diseases such as diabetes and hypertension with effective medicines and healthcare services can save lives and reduce complications, yet many people do not receive guideline-recommended care.[1–3] One important barrier to optimal care is cost related nonadherence which was reported by 9.6% of people who had received a prescription in the past year. [4] Cost related nonadherence could undermine the provision of healthcare services as people may avoid participating in care if they cannot afford prescribed medicines.[4,5]

Many strategies have been tested to improve the process of care for chronic diseases, with varying success. Resource intensive interventions such as financial incentives to providers and multidisciplinary changes to the primary care team are associated with modest improvements in diabetes and hypertension management.[6,7] Caring for patients with chronic diseases is expensive. [8] The cost and effectiveness of interventions to improve guideline-recommended care are important to consider, since increasing access to effective treatments may reduce costs related to complications, but may increase per-patient costs related to clinicians' monitoring of treatments and more expensive health technologies. [9]

We recently completed the Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial, a randomized controlled trial in which patients with self-reported cost-related medication nonadherence were randomly assigned to receive free distribution of medicines from a comprehensive list of essential medicines.[10] The CLEAN Meds trial found that providing Canadian primary care patients with medicines at no charge improved adherence to medication and, for patients with diabetes and hypertension, chronic disease management was improved based on some surrogate outcomes.[10] As previously reported, with free distribution of medicines, hemoglobin A1c levels were 0.4 % lower (95 % CI -0.76 to 0.0) compared with usual access, and systolic blood pressure was 7 mmHg lower (95% CI -11.7 to -2.8) compared with usual access. Given the importance of medication related adherence in patients with chronic diseases, in this post-hoc analysis, we tested the impact on diabetes and

1
2
3 hypertension process of care indicators of providing free access to medicine to people with diabetes and
4
5 hypertension.
6
7

8 9 **METHODS**

10 11 **Patients**

12 We identified patients in the CLEAN Meds trial with diabetes (with or without hypertension) or only
13 hypertension by identifying all participants prescribed at least one diabetic or anti-hypertensive agent at
14 the start of the trial. Randomization was not stratified based on these conditions. Patients prescribed both
15 a diabetic agent and an anti-hypertensive agent were included only in the diabetes group.
16
17
18
19
20
21
22
23

24 25 **Process of Care Indicators**

26 Using the care goals of diabetes and the Diabetes Canada Guidelines [11] we identified the following
27 process of care indicators for the management of diabetes: encounters with healthcare professionals [in-
28 clinic appointments and telephone appointments with primary care physicians or nurse practitioners],
29 blood pressure measurements, self-monitoring of blood glucose, annual eye exam (with an optometrist or
30 ophthalmologist), foot screening exams (foot care and/or neuropathy screening), annual administration of
31 the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and
32 urine albumin to creatinine ratio (ACR).[11] Glycated hemoglobin (HbA1c) and self-monitoring blood
33 glucose (SMBG) can be used as indicators for the management of glycemic control.
34
35
36
37
38
39
40
41
42
43
44

45 Using the guidelines and the goals of care for hypertension and the Hypertension Canada Guidelines, [12]
46 we identified the following process of care indicators for the management of hypertension: encounters
47 with healthcare professionals, blood pressure measurements, self-measuring of blood pressure (at home or
48 at the pharmacy), and serum tests for electrolytes, HbA1c, lipids, and creatinine.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Since a number of the recommended clinical manoeuvres and other aspects of care (e.g. medicine
4 adjustments) involve patients interacting with healthcare providers, we also assess healthcare encounters
5 that included in person visits and telephone encounters with primary care physicians or nurse practitioners
6 where diabetes or hypertension were documented as being discussed.
7
8
9
10

11 12 13 **Data Collection**

14
15 Using the PSS Suite software [13], chart extractions were performed for all patients to record the
16 identified process of care indicators for diabetes and hypertension respectively. Two abstracters (OC,
17 HW) were blinded to the patients' intervention status at the time of chart extraction. To ensure reliability
18 of chart extraction, each abstracter completed 5 chart extractions independently and compared findings;
19 there were no disagreements. OC, HW and MA then completed the chart extraction for all participants.
20
21
22
23
24
25
26
27

28 For all patients with diabetes, starting from the patient's start date in the trial to one year later, the
29 following information was recorded from each chart: number of encounters with primary care physicians
30 and nurse practitioners related to diabetes (in-person visits and phone calls were included), number of
31 missed primary care appointments (this is tracked and missed appointments are explicitly stated in the
32 EMR), number of consultant (specialist physician) encounters related to diabetes, number of blood
33 pressure measurements performed at healthcare visits, number of serum hemoglobin A1c (HbA1c)
34 measurements, number of serum LDL-cholesterol (LDL-c) measurements, if serum creatinine (Cr) was
35 measured (binary; done during the year or not), if urine albumin to creatinine ratio (ACR) was measured
36 (binary), if the patient self-monitored their blood glucose levels (binary), if an annual eye screening exam
37 was performed (binary), if an annual foot screening exam was performed (binary), and if the annual
38 influenza vaccine was administered (binary). We also recorded the number of new diabetes medicines
39 each diabetic patient was prescribed and the number of diabetes medicines they stopped taking, during the
40 one year study period. All of this information was found in the charts as expected, however, flu vaccines
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 may have been given elsewhere, such as at a pharmacy, and may not have been fully captured in chart
4
5 review.
6
7
8
9
10

11 For all patients with hypertension, starting from the patient's start date in the trial to one year later, the
12 following information was recorded: total number of encounters with primary care physicians and nurse
13 practitioners, number of consultant appointments related to hypertension, number of missed primary care
14 appointments, number of blood pressure measurements performed at healthcare visits; number of serum
15 electrolyte tests [any number of the following tests were included: Na, K, Cl, HCO₃⁻ and if a patient had
16 NA, K and Cl done on the same day, this was counted as one electrolyte test], number of serum HbA_{1c}
17 measurements, number of serum lipid measurements (any number of the following tests were included:
18 LDL-c, HDL-c, non-HDL-c, triglycerides, cholesterol), number of serum creatinine (Cr) measurements,
19 if the patient self-measures their blood pressure either at home or at a community pharmacy (binary), and
20 the number of new hypertension medicines each patient was prescribed and stopped taking. This
21 information was found in the charts as expected.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 **Data Analysis**

38 For clinical manoeuvres that are recommended to be performed multiple times during one year (e.g. blood
39 pressure measurements) and for encounters with healthcare professionals we report the rate ratios with
40 95% confidence intervals that were estimated using a Poisson regression model. We report unadjusted
41 rate ratios and rate ratios adjusted for age, sex and clinic location (urban versus rural). We compared the
42 proportion of patients in each arm receiving clinical manoeuvres that are recommended to be done only
43 once during a one-year period (e.g. annual eye examination for people with diabetes) and report the odds
44 ratio with 95% confidence intervals that was estimated using a logistic regression model. We report
45 unadjusted odds ratios and odds ratios adjusted for age, sex and location (urban versus rural). No p-value
46 threshold was set for these post-hoc and hypothesis generating analyses.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

We also compared the net change in medications for hypertension and diabetic patients in the intervention and control arms.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline characteristics

Of the 786 patients enrolled in the CLEAN Meds trial, 163 patients were prescribed one or more medicines for diabetes and were included in the diabetes group [including 114 who were also prescribed one or more anti-hypertensive agents], and 105 patients were nondiabetic and prescribed one or more anti-hypertensive agents and included in the hypertension group. We thus included 268 participants in this study. Of the 163 patients with diabetes, 83 patients were in the intervention group receiving free distribution of medicines, while the remaining 80 patients were in the control group receiving standard access to medicines. Of the 105 patients with hypertension, 56 patients were in the intervention group receiving free distribution of medicines, and 49 patients were in the control group receiving standard access to medicines.

Figure 1. Flowchart illustrating study participant inclusion

For this posthoc analysis, the groups are balanced with the exception of hypertension in urban and rural groups. The characteristics of participants in the diabetes and hypertension groups are summarized in Table 1.

Table 1. Baseline participant characteristics.

	Diabetes [n = 163]	Hypertension [n = 105]
--	---------------------------	-------------------------------

	Free distribution Number [%] [n = 83]	Usual access Number [%] [n = 80]	Free distribution Number [%] [n = 56]	Usual access Number [%] [n = 49]
Women	35 [42.2]	35 [43.8]	22 [39.3]	17 [34.7]
Age [mean, SD]	59 ± 10	58 ± 11.2	60 ± 8.2	61 ± 9.3
Age 65 years or older	25 [30.1]	19 [23.8]	17 [30.4]	16 [32.7]
Ethnicity				
White	42 [50.6]	53 [66.3]	46 [82.1]	34 [69.4]
Black	9 [10.8]	10 [12.5]	2 [3.6]	4 [8.1]
Southeast or East Asian [incl Korean, Japanese, Filipino, Chinese]	6 [7.2]	2 [2.5]	4 [7.1]	2 [4.1]
South Asian	14 [16.9]	9 [11.3]	1 [1.8]	3 [6.1]
Latin American	1 [1.2]	3 [3.8]	0 [0.0]	2 [4.1]
West Asian [including Arab]	2 [2.4]	1 [1.3]	0 [0.0]	0 [0.0]
Mixed or other	9 [10.8]	2 [2.5]	2 [3.6]	4 [8.2]
Declined to provide	0 [0.0]	0 [0.0]	4 [7.1]	0 [0.0]
Main Income source				
Wages and salaries [including self-employed]	44 [53.0]	38 [47.5]	30 [53.6]	28 [57.1]
Pension	22 [26.5]	19 [23.8]	14 [25.0]	9 [18.4]
Social support [e.g. welfare or disability]	11 [13.3]	13 [16.3]	4 [7.1]	8 [16.3]
Unemployment insurance	4 [4.8]	3 [3.8]	4 [7.1]	2 [4.1]
Other	0 [0.0]	1 [1.3]	0 [0.0]	0 [0.0]
Declined to provide	2 [2.4]	6 [7.5]	4 [7.1]	2 [4.1]
Household income*				
\$30 000 CAD or less	46 [55.4]	41 [51.3]	23 [41.1]	19 [38.8]
\$30 000 to 70 000	24 [28.9]	22 [27.5]	12 [21.4]	12 [24.5]
\$70 000 or greater	3 [3.6]	4 [5.0]	4 [7.1]	0 [0.0]
Declined to provide	10 [12.0]	13 [16.3]	17 [30.4]	18 [36.7]
Number of medicines prescribed at baseline [mean, SD]	5 ± 2.8	5 ± 3.1	4 ± 2.0	4 ± 2.6
Urban site	50 [60.2]	48 [60.0]	22 [39.3]	27 [55.1]
Rural site	33 [39.8]	32 [40.0]	34 [60.7]	22 [44.9]

Impact of free distribution of medicines in subgroup of people with diabetes

For patients with diabetes, there was a trend toward slightly more self-monitoring of blood glucose (aRR 1.3; 95 % CI 0.7-2.6; $p = 0.45$) and small increases in rates of serum creatinine measurement (aOR 1.3; 95 % CI 0.6-2.9; $p = 0.48$) but not hemoglobin A1c measurements (aRR 1.1; 95 % CI; 0.9-1.3; $p = 0.44$) for patients receiving free distribution compared to those with usual medicine access (see Table 2). There were no differences in appointments with primary care providers or consultants, but there was a trend toward fewer missed appointments with primary care providers (aRR 0.8; 95 % CI 0.5-1.3; $p = 0.39$) (see Table 2). There was no difference between the free distribution and usual access groups with respect to net change in medicine prescriptions. Overall, the net change in the number of medicines prescribed to participants receiving free distribution was 14 new starts (a total of 19 new medicines started and 5 medicines stopped; average of 0.17 new medicines per person) and the net change for those with usual access was 14 new starts (a total of 21 new medicines started and 7 medicines stopped; average of 0.18 new medicines per person).

Table 2. Diabetes process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
Hemoglobin A1c measurements	2 [1-3] [187]	2 [1-3] [160]	1.1 [0.9-1.4] $p = 0.27$	1.1 [0.9-1.3] $p = 0.44$
BP measurements	3 [2-5] [278]	3 [2-4] [274]	1.0 [0.8-1.2] $p = 0.85$	1.0 [0.8-1.2] $p = 0.71$
LDL-c measurements	1 [0-1] [65]	1 [0-1] [61]	1.0 [0.7-1.5] $p = 0.88$	1.0 [0.7-1.4] $p = 0.96$
Urine ACR measured	54 % [45/83]	58 % [46/80]	0.9 [0.5-1.6] $p = 0.67$	0.9 [0.5-1.7] $p = 0.70$
Serum creatinine measured	82 % [68/83]	76 % [61/80]	1.4 [0.7- 3.0] $p = 0.37$	1.3 [0.6-2.9] $p = 0.48$
Foot examination performed	63 % [52/83]	61 % [49/80]	1.1 [0.6-2.0] $p = 0.85$	0.9 [0.5-1.8] $p = 0.87$
Eye examination performed	42 % [35/83]	43 % [34/80]	1.0 [0.5-1.8] $p = 0.97$	1.0 [0.5-2.0] $p = 0.93$

Influenza vaccine administered	29 % [24/83]	28 % [22/80]	1.1 [0.5-2.1] p = 0.84	1.1 [0.5-2.2] p = 0.84
Self-monitoring of blood glucose	54 % [45/83]	48 % [38/80]	1.3 [0.7-2.4] p = 0.39	1.3 [0.7-2.6] p = 0.45
Primary care encounters related to diabetes	3 [1-5] [258]	3 [1-4] [243]	1.0 [0.8-1.3] p = 0.85	1.0 [0.8-1.3] p = 0.90
Consultant encounters related to diabetes	0 [0-1] [49]	0 [0-1] [51]	0.9 [0.5-1.6] p = 0.79	1.0 [0.6-1.8] p = 0.96
Missed primary care appointments	0 [0-1] [43]	0 [0-1] [49]	0.9 [0.5- 1.4] p = 0.54	0.8 [0.5-1.3] p = 0.39
Total number of encounters and manoeuvres [assign 0 or 1 for binary indicators; exclude missed appointments]	11 [9-17] [1039]	12 [9-16] [1106]	1.0 [0.9-1.2] p = 0.74	1.0 [0.9 to 1.2] p = 0.85

Count indicators are reported as the median number of measurements or encounters with the IQR and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as rate ratio or odds ratio with the 95% confidence interval and p value.

Impact of free distribution of medicines in subgroup of people with hypertension

Among hypertension patients, free distribution was associated with less serum creatinine [aRR 0.6; 95 % CI 0.4 -1.0; p = 0.04] and electrolyte measuring (aRR 0.6; 95 % CI 0.4-1.0; p = 0.04) and fewer missed appointments (aRR 0.4; 95 % CI 0.2-0.9; p = 0.03) (see Table 3). There were trends towards fewer encounters with primary care providers (aRR 0.9; 0.7-1.1; p = 0.25) and consultants (aRR 0.6; 95 % CI 0.1-4.6; p = 0.61) but similar self-monitoring of blood pressure (aOR 1.1; 95 % CI 0.4-3.2; p = 0.86) (see Table 3). There was no difference in blood pressuring measuring in clinic. There were slightly more new medicine starts in participants receiving free distribution. Overall, the net change in the number of medicines prescribed to intervention participants was 15 new starts (a total of 20 new medicines started

and 5 medicines stopped; average: 0.27 new medicines per person) and the net change for control participants was 0 (a total of 9 new medicines started and 9 medicines stopped).

Table 3. Hypertension process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
BP measurements	3 [2-4] [173]	3 [2-4] [160]	1.0 [0.7- 1.2] p = 0.67	1.00 [0.8-1.3] p = 0.92
Hemoglobin A1c measurements	0 [0-1] [37]	1 [0-1] [42]	0.8 [0.5- 1.2] p = 0.27	0.8 [0.5-1.3] p = 0.41
Lipid measurements	0 [0-1] [36]	1 [0-1] [37]	0.9 [0.5- 1.4] p = 0.49	0.9 [0.6-1.5] p = 0.70
Serum creatinine measurements	1 [0-1.3] [78]	1 [0-3] [110]	0.6 [0.4- 1.0] p = 0.05	0.6 [0.4 -1.0] p = 0.04
Serum electrolyte measurements	1 [0-1] [66]	1 [0-3] [103]	0.6 [0.3-0.9] p = 0.02	0.6 [0.4-1.0] p = 0.04
Primary care encounters	5 [3-7] [287]	5 [3-9] [302]	0.8 [0.7-1.1] p = 0.11	0.9 [0.7-1.1] p = 0.25
Consultant encounters related to hypertension	0 [0-0] [5]	0 [0-1] [5]	0.9 [0.1-6.1] p = 0.89	0.6 [0.1-4.6] p = 0.61
Missed primary care appointments	0 [0-0] [14]	0 [0-1] [44]	0.3 [0.1- 0.6] p = 0.00	0.4 [0.2-0.9] p = 0.03
Self-monitoring of blood pressure	21 % [12/56]	18 % [9/49]	1.2 [0.5-3.2] p = 0.70	1.1 [0.4-3.2] p = 0.86
Total number of encounters and manoeuvres [assign 0 or 1 for binary indicators; exclude missed appointments]	12 [8-15] [694]	15 [8-20] [768]	0.8 [0.6-1.0] p = 0.04	0.8 [0.7-1.0] p = 0.10

Count indicators are reported as the median number of measurements or encounters with the IQR and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as odds ratio or rate ratio with the 95% confidence interval and p value.

DISCUSSION

In this post-hoc analysis of randomized controlled trial findings, free distribution of medicines to people with diabetes or hypertension was not associated with more visits to primary care providers or consultants and, in fact, patients with hypertension had less laboratory monitoring and slightly fewer visits. Free distribution may slightly increase self-monitoring and reduce missed appointments.

The modest reductions in laboratory testing of serum creatinine and electrolytes for patients with hypertension may reflect appropriate clinical judgement against repeat testing. The Canadian guidelines recommend that the frequency of laboratory testing should be guided by clinical judgement and no specific intervals are mentioned in the guidelines. Clinicians may have been less likely to order laboratory testing in patients receiving free distribution because they had slightly better control of their blood pressure, possibly due to the greater number of medicines prescribed. These tests may also have been ordered less frequently because patients had fewer visits, potentially because they were self-monitoring. Systematic reviews have reported improved glycemic control in diabetic patients performing self-monitoring of blood glucose, and reduced blood pressure in patients with hypertension self-measuring their blood pressure.[14,15] Thus, the observed trend towards more self-monitoring, if real, could reflect improved patient motivation, better disease control, or different guidance from clinicians. A 2018 randomized controlled trial found that using self-monitored blood pressure readings to titrate anti-hypertensive treatments led to a significant reduction in blood pressure compared to the use of clinic readings to guide care.[16] In this trial, patients with hypertension had substantially better blood pressure control. The improvements in disease control and usefulness of self-measured blood pressure readings may have resulted in clinicians asking patients to monitor their blood pressure at home rather than attend clinic; this would explain both the increase in self-monitoring and the reduction in clinic visits. A 1985 controlled trial of the effects of medical insurance on health spending and health status reported lower

1
2
3 blood pressure with free care, though the cause of the difference was additional contact with physicians
4
5 under free care. [17]
6
7
8

9 The reduction in missed appointments observed here may be explained by an improved clinician-patient
10 relationship and better perceived disease control. The reduction in missed appointments did not relate to
11 needing to attend appointments in order to get their free medications, as the study pharmacist had access
12 to their electronic medical record, could communicate with primary care providers, and medications were
13 mailed to participants. A 2004 study of patient perceptions found that emotional barriers [including the
14 fear of bad news] and perceived disrespect by the healthcare system caused patients to miss primary care
15 appointments.[18] Additionally, a 2014 cross-sectional survey reported that patients with hypertension
16 with no medication coverage and high medication costs were more likely to miss appointments.[19]
17
18

19 Patients may not take their medicines due to cost and may miss appointments due to feelings of
20 embarrassment or guilt over this; this may be obviated by free distribution of medicines.
21
22
23
24
25

26 Our study found that there was only a small non-significant increase in hemoglobin A1c monitoring and
27 serum creatinine monitoring in patients with diabetes. Our findings suggest that financial barriers to
28 medication access may not deter patients with diabetes from engaging in necessary health visits and
29 screening related to the management of their condition. In contrast, a study of American patients with
30 diabetes found that lower cost-related nonadherence was associated with improved compliance to annual
31 diabetes recommendations.[5] Financial incentives to clinicians, audit and feedback interventions, and
32 reminders to clinicians can achieve modest reductions in hemoglobin A1c, and our study found a small
33 increase in the frequency of HbA1c monitoring with free medicine distribution.[6]
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 The results of this study post-hoc analysis of trial findings suggest that improving access to chronic
50 disease medicines will not substantially increase costs associated with outpatient visits. To the contrary,
51 in this study free distribution appeared to increase self-monitoring, reduce visits for hypertension and
52 reduce the total number of healthcare encounters and manoeuvres performed in a year, without changing
53
54
55
56
57
58
59
60

1
2
3 the likelihood of visits for diabetes. Increasing access to medicines may encourage self-monitoring
4 practices, reduce in-person visits, and decrease laboratory investigations performed. Free distribution of
5 medicines may not only improve blood pressure control but could also reduce the per-person costs
6 associated with the management of hypertension.
7
8
9
10

11
12
13 Strengths of this study include the fact that the results are based on a randomized controlled trial.

14
15 Participants differed with respect to income level, ethnicity and location (urban versus rural). Despite the
16 fact that this was a post-hoc analysis and randomization was not stratified based on these characteristics,
17 we found that the groups were largely balanced; except for urban status. There are also some limitations
18 in this analysis. Associations identified during post-hoc analyses could be spurious and thus the findings
19 should be viewed as hypothesis-generating.[20] The trial was not designed to have sufficient power to
20 detect differences in some of the outcomes examined in this study so the failure to identify associations
21 should be interpreted with caution. Since the trial was unblinded, patients and clinicians could have been
22 motivated by allocation to free access to improve the process of care. The trial was conducted with
23 primary care patients in a high-income country who reported cost-related non-adherence and the findings
24 may not apply in other settings. The study was based on a review of primary care charts that do not
25 reflect every actual encounter (e.g. visits to other providers).
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **CONCLUSION**

42
43 This post-hoc analysis of randomized controlled trial results found that free distribution of medicines may
44 improve self-monitoring behaviours and reduce missed primary care appointments for patients with
45 diabetes or hypertension. Free distribution may also reduce primary care and consultant appointments and
46 laboratory testing in patients with hypertension. Additionally, free distribution of medicines improves
47 disease control and improves patients' self-reported care. [21] Overall, these findings suggest that
48 improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate
49 health outcomes but also improves the patient experience and may also reduce healthcare costs by
50
51
52
53
54
55
56
57
58
59
60

1
2
3 encouraging self-monitoring practices. The hypotheses generated by this post-hoc analysis of randomized
4 controlled trial findings could be tested in future studies.
5
6
7

8 9 **FUNDING STATEMENT**

10
11 This work was supported by the Canadian Institutes of Health Research and the Keenan Research Summer
12 Student Program. They played no role in study design; in the collection, analysis and interpretation of data;
13 in the writing of the report; and in the decision to submit the article for publication.
14
15
16
17

18 19 **COMPETING INTERESTS STATEMENT**

20
21 NP reports grants from Canadian Institutes for Health Research, the Ontario SPOR Support Unit, the
22 Canada Research Chairs program and Physicians Services Incorporated during the conduct of the study.
23
24 All other authors (OC, HW, MA, BM and BS) declare that they have no competing interests.
25
26
27
28
29

30 31 **AUTHOR CONTRIBUTIONS**

32
33 OC contributed to the data curation, formal analysis, investigation, methodology, visualization, writing the
34 original draft and reviewing and editing. HW contributed to the data curation, formal analysis, investigation,
35 writing the original draft and reviewing and editing. MA contributed to the data curation, formal analysis,
36 and reviewing and editing. BM contributed to the methodology, validation, investigation, resources and
37 reviewing and editing. BS contributed to the methodology, validation, investigation, resources and
38 reviewing and editing. NP contributed to the conceptualization, methodology, validation, formal analysis,
39 investigation, resources, writing the original draft, reviewing and editing.
40
41
42
43
44
45
46
47
48
49

50 51 **DATA AVAILABILITY**

52 Deidentified participant data is available upon reasonable request from the corresponding author.
53
54
55
56
57
58
59
60

References

- [1] Braga M, Casanova A, Teoh H, Dawson KC, Gerstein HC, Fitchett DH, et al. Treatment gaps in the management of cardiovascular risk factors in patients with type 2 diabetes in Canada. *Can J Cardiol*. 2010 Jul;26[6]:297–302.
- [2] Saaddine JB, Engelgau MM, Beckles GL, Gregg EW, Thompson TJ, Narayan KMV. A Diabetes Report Card for the United States: Quality of Care in the 1990s. *Ann Intern Med*. 2002 Apr 16;136[8]:565.
- [3] Hajjar I, Kotchen TA. Trends in Prevalence, Awareness, Treatment, and Control of Hypertension in the United States, 1988-2000. *JAMA*. 2003 Jul 9;290[2]:199–206.
- [4] Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *Can Med Assoc J CMAJ Ott*. 2012 Feb 21;184[3]:297–302.
- [5] Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract*. 2018 Sep;143:24–33.
- [6] Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet Lond Engl*. 2012 Jun 16;379[9833]:2252–61.

- 1
2
3 [7] Walsh JME, McDonald KM, Shojania KG, Sundaram V, Nayak S, Lewis R, et al. Quality
4 improvement strategies for hypertension management: a systematic review. *Med Care*. 2006
5 Jul;44[7]:646–57.
6
7 [8] Rosella LC, Lebenbaum M, Fitzpatrick T, O’Reilly D, Wang J, Booth GL, et al. Impact of diabetes
8 on healthcare costs in a population-based cohort: a cost analysis. *Diabet Med J Br Diabet Assoc*.
9 2016 Mar;33[3]:395–403.
10
11 [9] Weaver CG, Clement FM, Campbell NRC, James MT, Klarenbach SW, Hemmelgarn BR, et al.
12 Healthcare Costs Attributable to Hypertension: Canadian Population-Based Cohort Study.
13 *Hypertens Dallas Tex 1979*. 2015 Sep;66[3]:502–8.
14
15 [10] Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment
16 Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized
17 Clinical Trial. *JAMA Intern Med [Internet]*. 2019 Oct 7 [cited 2019 Oct 31]; Available from:
18 <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2752366>
19
20 [11] Diabetes Canada | Clinical Practice Guidelines - 2018 Full Guidelines [Internet]. [cited 2019 Sep
21 23]. Available from: <http://guidelines.diabetes.ca/cpg>
22
23 [12] Diagnosis & Assessment | Hypertension Canada Guidelines [Internet]. [cited 2019 Sep 23].
24 Available from: <https://guidelines.hypertension.ca/diagnosis-assessment/>
25
26 [13] Telus. PS Suite EMR.
27
28 [14] Zhu H, Zhu Y, Leung S. Is self-monitoring of blood glucose effective in improving glycaemic
29 control in type 2 diabetes without insulin treatment: a meta-analysis of randomised controlled trials.
30 *BMJ Open*. 2016 Sep 1;6[9]:e010524.
31
32 [15] Uhlig K, Patel K, Ip S, Kitsios GD, Balk EM. Self-measured blood pressure monitoring in the
33 management of hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2013 Aug
34 6;159[3]:185–94.
35
36 [16] McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J, et al. Efficacy of self-
37 monitored blood pressure, with or without telemonitoring, for titration of antihypertensive
38 medication [TASMINH4]: an unmasked randomised controlled trial. *The Lancet*. 2018 Mar
39 10;391[10124]:949–59.
40
41 [17] Keeler EB, Brook RH, Goldberg GA, Kamberg CJ, Newhouse JP. How Free Care Reduced
42 Hypertension in the Health Insurance Experiment. *JAMA*. 1985 Oct 11;254[14]:1926–31.
43
44 [18] Lacy NL, Paulman A, Reuter MD, Lovejoy B. Why We Don’t Come: Patient Perceptions on No-
45 Shows. *Ann Fam Med*. 2004 Nov;2[6]:541–5.
46
47 [19] Nwabuo CC, Dy SM, Weeks K, Young JH. Factors associated with appointment non-adherence
48 among African-Americans with severe, poorly controlled hypertension. *PloS One*.
49 2014;9[8]:e103090.
50
51 [20] Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and
52 baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med*.
53 2002;21[19]:2917–30.
54
55
56
57
58
59
60

- 1
2
3 [21] Persaud N, Bedard M, Boozary A, Glazier RH, Gomes T, Hwang SW, et al. Effects of distributing
4 essential medications at no charge: results of a multicentre, unmasked, randomised controlled study.
5 JAMA Intern Med.
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

For peer review only

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

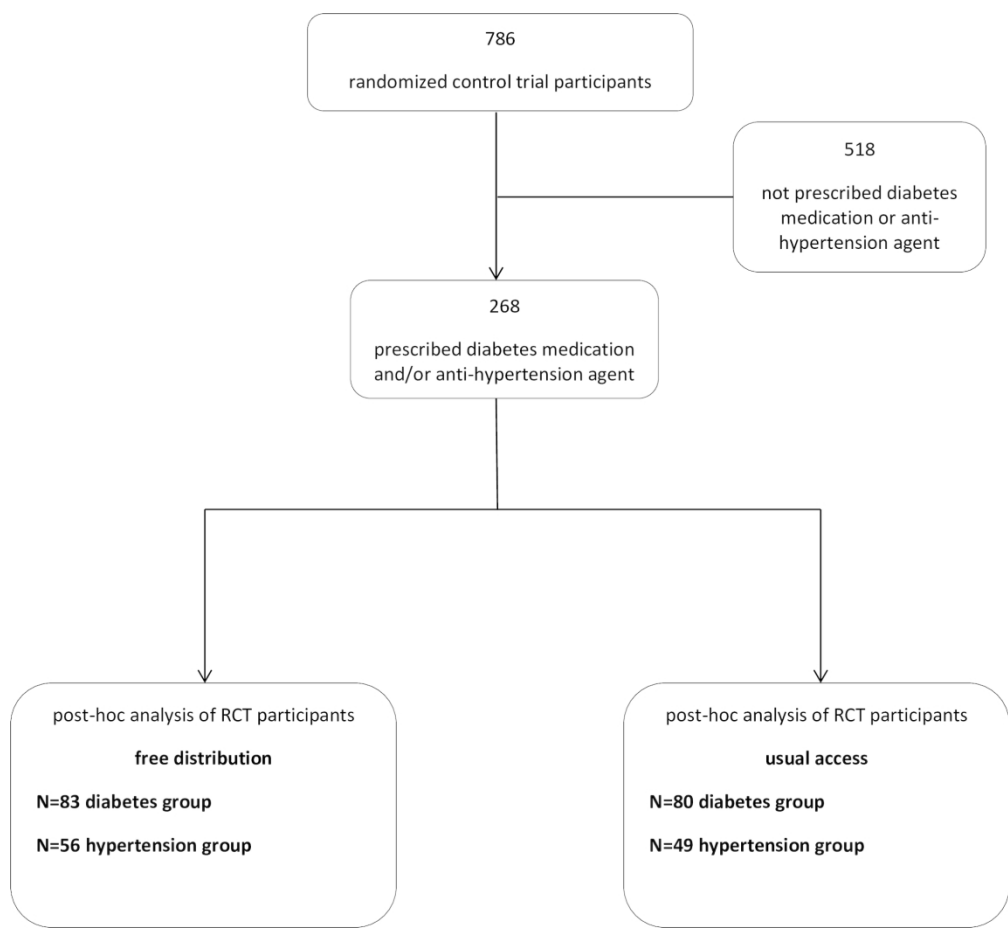


Figure 1. Flowchart illustrating study participant inclusion

190x173mm (300 x 300 DPI)

BMJ Open

Effect of free distribution of medicines on the process of care for adult patients with type 1 and type 2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042046.R1
Article Type:	Original research
Date Submitted by the Author:	16-Dec-2020
Complete List of Authors:	Charles, Onella; University of Toronto Faculty of Medicine; St Michael's Hospital Centre for Urban Health Solutions Woods, Hannah; St Michael's Hospital Centre for Urban Health Solutions Ally, Muhamad; St Michael's Hospital Centre for Urban Health Solutions Manns, Braden; University of Calgary Cumming School of Medicine, Department of Community Health Sciences ; University of Calgary Cumming School of Medicine, Department of Medicine Shah, Baiju; University of Toronto Institute of Health Policy Management and Evaluation; Institute for Clinical Evaluative Sciences Persaud, Nav; St. Michael's Hospital, Li Ka Shing Knowledge Institute
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health policy
Keywords:	DIABETES & ENDOCRINOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effect of free distribution of medicines on the process of care for adult patients with type 1 and type 2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings

Onella Charles BSc^{1,2}, Hannah M Woods MSc², Muhamad Z Ally BSc², Braden Manns MD^{5, 6, 7, 8}, Baiju R Shah MD^{3, 9, 10, 11}, Nav Persaud MD^{2, 3, 4, 9}.

¹ Faculty of Medicine, University of Toronto, 1 King's College Cir, Toronto, ON, Canada

² MAP Centre for Urban Health Solutions, St. Michael's Hospital, 30 Bond St, Toronto, ON, Canada

³ Department of Family and Community Medicine, University of Toronto, 500 University Ave, Toronto, ON, Canada

⁴ Department of Family and Community Medicine, St. Michael's Hospital, 80 Bond st, Toronto, ON, Canada

⁵ Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁶ Department of Medicine, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁷ O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, 3280 Hospital Dr NW, Calgary, AB, Canada

⁸ Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada

⁹ Institute of Health Policy, Management, and Evaluation, University of Toronto, 155 College St, Toronto, ON, Canada

¹⁰ Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Toronto, ON, Canada

¹¹ Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON, Canada

Corresponding author: Nav Persaud, 80 Bond St. Toronto, Ontario, Canada M5B 1X2
Nav.persaud@utoronto.ca 416-864-6060 Ext 775778

Key Words: Essential medicine; diabetes; process of care; health outcome

Wordcount: 2981 **Figures:** 1 **Tables:** 3

ABSTRACT

Objectives

The Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial randomized controlled trial showed that patients receiving free access to medicines had improved diabetes and hypertension outcomes compared to patients who had usual access to medicines. In this study, we aimed to test the impact of providing free access to medicine to people with diabetes and hypertension on process of care indicators.

Design

In this post hoc analysis of randomized controlled trial findings we identified process of care indicators for the management of diabetes and hypertension using relevant guidelines. The follow process of care indicators were identified for diabetes management: encounters with healthcare professionals, blood pressure measurements, self-monitoring of blood glucose, annual eye and foot exam, annual administration of the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and urine albumin to creatinine ratio (ACR). We identified the following process of care indicators for hypertension: encounters with healthcare professionals, blood pressure measurements, self-measuring of blood pressure, and serum tests for electrolytes, HbA1c, lipids, and creatinine. Chart extractions were performed for all patients and the indicators for diabetes and hypertension were recorded. We compared the indicators for patients in each arm of the trial.

Results

The study included 268 primary care patients. Free distribution of medicines may improve self-monitoring behaviours (aRR 1.3; 95 % CI 0.7-2.6) and reduce missed primary care appointments for patients with diabetes (aRR 0.8; 95 % CI 0.5-1.3) or hypertension (aRR 0.4; 95 % CI 0.2-0.9). Free distribution may also reduce primary care and consultant appointments and laboratory testing in patients with hypertension.

Conclusions

Improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate health outcomes but also improves the patient experience and may also reduce healthcare costs by encouraging self-monitoring.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study is based on a randomized controlled trial.
- Despite the fact that this was a post-hoc analysis and randomization was not stratified based on these characteristics, we found that the groups were largely balanced.
- Associations identified during post-hoc analyses could be spurious and thus the findings should be viewed as hypothesis-generating.
- The trial this study was based on was conducted with primary care patients in a high-income country who reported cost-related non-adherence and the findings may not apply in other settings.

INTRODUCTION

Managing people with chronic diseases such as diabetes and hypertension with effective medicines and healthcare services can save lives and reduce complications, yet many people do not receive guideline-recommended care.[1–3] One important barrier to optimal care is cost related nonadherence which was reported by 9.6% of people who had received a prescription in the past year. [4] Cost related nonadherence could undermine the provision of healthcare services as people may avoid participating in care if they cannot afford prescribed medicines.[4,5]

Many strategies have been tested to improve the process of care for chronic diseases, with varying success. Resource intensive interventions such as financial incentives to providers and multidisciplinary changes to the primary care team are associated with modest improvements in diabetes and hypertension management.[6,7] Caring for patients with chronic diseases is expensive. [8] The cost and effectiveness of interventions to improve guideline-recommended care are important to consider, since increasing access to effective treatments may reduce costs related to complications, but may increase per-patient costs related to clinicians' monitoring of treatments and more expensive health technologies. [9]

We recently completed the Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial, a randomized controlled trial in which patients with self-reported cost-related medication nonadherence were randomly assigned to receive free distribution of medicines from a comprehensive list of essential medicines.[10] The CLEAN Meds trial found that providing Canadian primary care patients with medicines at no charge improved adherence to medication and, for patients with diabetes and hypertension, chronic disease management was improved based on some surrogate outcomes.[10] As previously reported, with free distribution of medicines, hemoglobin A1c levels were 0.4 % lower (95 % CI -0.76 to 0.0) compared with usual access, and systolic blood pressure was 7 mmHg lower (95% CI -11.7 to -2.8) compared with usual access. We undertook this post-hoc analysis both to help understand

1
2
3 why the intervention was beneficial in some circumstances and why the intervention did not have a large
4 benefit in general or any benefit for some participants. Given the importance of medication related
5 adherence in patients with chronic diseases, in this post-hoc analysis, we tested the impact on diabetes and
6 hypertension process of care indicators of providing free access to medicine to people with diabetes and
7 hypertension.
8
9
10
11
12
13
14
15
16
17
18
19

20 **METHODS**

21 **Patients**

22 We identified patients in the CLEAN Meds trial with diabetes (with or without hypertension) or only
23 hypertension by identifying all participants prescribed at least one diabetic or anti-hypertensive agent at
24 the start of the trial. Randomization was not stratified based on these conditions. Because anti-
25 hypertensives such as ACE inhibitors and angiotensin receptor blockers are a standard part of diabetes
26 management (even when blood pressure is “normal”), we included patients who were prescribed both a
27 diabetic agent and an anti-hypertensive agent only in the diabetes group.
28
29
30
31
32
33
34
35
36
37
38

39 **Process of Care Indicators**

40 Using the care goals of diabetes and the Diabetes Canada Guidelines [11] we identified the following
41 process of care indicators for the management of diabetes: encounters with healthcare professionals [in-
42 clinic appointments and telephone appointments with primary care physicians or nurse practitioners],
43 blood pressure measurements, self-monitoring of blood glucose, annual eye exam (with an optometrist or
44 ophthalmologist), foot screening exams (foot care and/or neuropathy screening), annual administration of
45 the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and
46 urine albumin to creatinine ratio (ACR).[11] Glycated hemoglobin (HbA1c) and self-monitoring blood
47 glucose (SMBG) can be used as indicators for the management of glycemic control.
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 Using the guidelines and the goals of care for hypertension and the Hypertension Canada Guidelines, [12]
6 we identified the following process of care indicators for the management of hypertension: encounters
7 with healthcare professionals, blood pressure measurements, self-measuring of blood pressure (at home or
8 at the pharmacy), and serum tests for electrolytes, HbA1c, lipids, and creatinine.
9
10
11
12
13
14
15

16 Since a number of the recommended clinical manoeuvres and other aspects of care (e.g. medicine
17 adjustments) involve patients interacting with healthcare providers, we also assess healthcare encounters
18 that included in person visits and telephone encounters with primary care physicians or nurse practitioners
19 where diabetes or hypertension were documented as being discussed.
20
21
22
23
24
25

26 **Data Collection**

27
28 Patients' primary care electronic medical records (EMRs) were accessed using the PS Suite software (an
29 EMR provider that is used by the sites from which trial participants were recruited) [13] and information
30 for the identified process of care indicators for diabetes and hypertension were identified and abstracted.
31
32
33

34 Two abstracters (OC, HW) were blinded to the patients' intervention status at the time of chart
35 abstraction. To ensure reliability of chart abstraction, each abstracter completed 5 chart abstractions
36 independently and compared findings; there were no disagreements. OC, HW and MA then completed
37 the chart abstractions for all participants.
38
39
40
41
42
43
44

45 For all patients with diabetes, starting from the patient's start date in the trial to one year later, the
46 following information was recorded from each chart: number of encounters with primary care physicians
47 and nurse practitioners related to diabetes (in-person visits and phone calls were included), number of
48 missed primary care appointments (this is tracked and missed appointments are explicitly stated in the
49 EMR), number of consultant (specialist physician) encounters related to diabetes, number of blood
50 pressure measurements performed at healthcare visits, number of serum hemoglobin A1c (HbA1c)
51
52
53
54
55
56
57
58
59
60

1
2
3 measurements, number of serum LDL-cholesterol (LDL-c) measurements, if serum creatinine (Cr) was
4 measured (binary; done during the year or not), if urine albumin to creatinine ratio (ACR) was measured
5 (binary), if the patient self-monitored their blood glucose levels (binary), if an annual eye screening exam
6 was performed (binary), if an annual foot screening exam was performed (binary), and if the annual
7 influenza vaccine was administered (binary). We also recorded the number of new diabetes medicines
8 each diabetic patient was prescribed and the number of diabetes medicines they stopped taking, during the
9 one year study period. All of this information was found in the charts as expected, however, flu vaccines
10 may have been given elsewhere, such as at a pharmacy, and may not have been fully captured in chart
11 review.
12
13
14
15
16
17
18
19
20
21
22
23
24
25

26 For all patients with hypertension, starting from the patient's start date in the trial to one year later, the
27 following information was recorded: total number of encounters with primary care physicians and nurse
28 practitioners, number of consultant appointments related to hypertension, number of missed primary care
29 appointments, number of blood pressure measurements performed at healthcare visits; number of serum
30 electrolyte tests [any number of the following tests were included: Na, K, Cl, HCO₃⁻ and if a patient had
31 NA, K and Cl done on the same day, this was counted as one electrolyte test], number of serum HbA_{1c}
32 measurements, number of serum lipid measurements (any number of the following tests were included:
33 LDL-c, HDL-c, non-HDL-c, triglycerides, cholesterol), number of serum creatinine (Cr) measurements,
34 if the patient self-measures their blood pressure either at home or at a community pharmacy (binary), and
35 the number of new hypertension medicines each patient was prescribed and stopped taking. This
36 information was found in the charts as expected.
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 **Data Analysis**

52 For clinical manoeuvres that are recommended to be performed multiple times during one year (e.g. blood
53 pressure measurements) and for encounters with healthcare professionals we report the rate ratios with
54
55
56
57
58
59
60

95% confidence intervals that were estimated using a Poisson regression model. We report unadjusted rate ratios and rate ratios adjusted for age, sex and clinic location (urban versus rural). We compared the proportion of patients in each arm receiving clinical manoeuvres that are recommended to be done only once during a one-year period (e.g. annual eye examination for people with diabetes) and report the odds ratio with 95% confidence intervals that was estimated using a logistic regression model. We report unadjusted odds ratios and odds ratios adjusted for age, sex and location (urban versus rural). No p-value threshold was set for these post-hoc and hypothesis generating analyses.

We also compared the net change in medications for hypertension and diabetic patients in the intervention and control arms. As part of the intervention, some patients had to switch medicines within a class. We thus used net changes as a measure that would treat both groups similarly and captured whether or not management had “intensified” by adding more agents.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline characteristics

Of the 786 patients enrolled in the CLEAN Meds trial, 163 patients were prescribed one or more medicines for diabetes and were included in the diabetes group [including 114 who were also prescribed one or more anti-hypertensive agents], and 105 patients were nondiabetic and prescribed one or more anti-hypertensive agents and included in the hypertension group. We thus included 268 participants in this study. Of the 163 patients with diabetes, 83 patients were in the intervention group receiving free distribution of medicines, while the remaining 80 patients were in the control group receiving standard access to medicines. Of the 105 patients with hypertension, 56 patients were in the intervention group

receiving free distribution of medicines, and 49 patients were in the control group receiving standard access to medicines. Study participant inclusion is illustrated in Figure 1.

Figure 1. Flowchart illustrating study participant inclusion

For this posthoc analysis, the groups are balanced with the exception of hypertension in urban and rural groups. The characteristics of participants in the diabetes and hypertension groups are summarized in Table 1.

Table 1. Baseline participant characteristics.

	Diabetes [n = 163]		Hypertension [n = 105]	
	Free distribution Number [%] [n = 83]	Usual access Number [%] [n = 80]	Free distribution Number [%] [n = 56]	Usual access Number [%] [n = 49]
Women	35 [42.2]	35 [43.8]	22 [39.3]	17 [34.7]
Age [mean, SD]	59 ± 10	58 ± 11.2	60 ± 8.2	61 ± 9.3
Age 65 years or older	25 [30.1]	19 [23.8]	17 [30.4]	16 [32.7]
Ethnicity				
White	42 [50.6]	53 [66.3]	46 [82.1]	34 [69.4]
Black	9 [10.8]	10 [12.5]	2 [3.6]	4 [8.1]
Southeast or East Asian [incl Korean, Japanese, Filipino, Chinese]	6 [7.2]	2 [2.5]	4 [7.1]	2 [4.1]
South Asian	14 [16.9]	9 [11.3]	1 [1.8]	3 [6.1]
Latin American	1 [1.2]	3 [3.8]	0 [0.0]	2 [4.1]
West Asian [including Arab]	2 [2.4]	1 [1.3]	0 [0.0]	0 [0.0]
Mixed or other	9 [10.8]	2 [2.5]	2 [3.6]	4 [8.2]
Declined to provide	0 [0.0]	0 [0.0]	4 [7.1]	0 [0.0]
Main Income source				
Wages and salaries [including self-employed]	44 [53.0]	38 [47.5]	30 [53.6]	28 [57.1]
Pension	22 [26.5]	19 [23.8]	14 [25.0]	9 [18.4]
Social support [e.g. welfare or disability]	11 [13.3]	13 [16.3]	4 [7.1]	8 [16.3]
Unemployment insurance	4 [4.8]	3 [3.8]	4 [7.1]	2 [4.1]
Other	0 [0.0]	1 [1.3]	0 [0.0]	0 [0.0]
Declined to provide	2 [2.4]	6 [7.5]	4 [7.1]	2 [4.1]

Household income*				
\$30 000 CAD or less	46 [55.4]	41 [51.3]	23 [41.1]	19 [38.8]
\$30 000 to 70 000	24 [28.9]	22 [27.5]	12 [21.4]	12 [24.5]
\$70 000 or greater	3 [3.6]	4 [5.0]	4 [7.1]	0 [0.0]
Declined to provide	10 [12.0]	13 [16.3]	17 [30.4]	18 [36.7]
Number of medicines prescribed at baseline [mean, SD]	5 ± 2.8	5 ± 3.1	4 ± 2.0	4 ± 2.6
Urban site	50 [60.2]	48 [60.0]	22 [39.3]	27 [55.1]
Rural site	33 [39.8]	32 [40.0]	34 [60.7]	22 [44.9]

Impact of free distribution of medicines in subgroup of people with diabetes

For patients with diabetes, there were small increases in rates of serum creatinine measurement (aOR 1.3; 95 % CI 0.6-2.9; p = 0.48) but not hemoglobin A1c measurements (aRR 1.1; 95 % CI; 0.9-1.3; p = 0.44) for patients receiving free distribution compared to those with usual medicine access. There no substantial difference in self-monitoring of blood glucose (aRR 1.3; 95% CI 0.7 – 2.6; p=0.45) (see Table 2). There were no differences in appointments with primary care providers or consultants, but there was a trend toward fewer missed appointments with primary care providers (aRR 0.8; 95 % CI 0.5-1.3; p = 0.39) (see Table 2). There was no difference between the free distribution and usual access groups with respect to net change in medicine prescriptions. Overall, the net change in the number of medicines prescribed to participants receiving free distribution was 14 new starts (a total of 19 new medicines started and 5 medicines stopped; average of 0.17 new medicines per person) and the net change for those with usual access was 14 new starts (a total of 21 new medicines started and 7 medicines stopped; average of 0.18 new medicines per person).

Table 2. Diabetes process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
Hemoglobin A1c measurements	2 [2] [187]	2 [2] [160]	1.1 [0.9-1.4] p = 0.27	1.1 [0.9-1.3] p = 0.44

BP measurements			1.0 [0.8-1.2] p = 0.85	1.0 [0.8-1.2] p = 0.71
	3 [7] [278]	3 [7] [274]		
LDL-c measurements			1.0 [0.7-1.5] p = 0.88	1.0 [0.7-1.4] p = 0.96
	1 [1] [65]	1 [1] [61]		
Urine ACR measured	54 % [45/83]	58 % [46/80]	0.9 [0.5-1.6] p = 0.67	0.9 [0.5-1.7] p = 0.70
Serum creatinine measured	82 % [68/83]	76 % [61/80]	1.4 [0.7- 3.0] p = 0.37	1.3 [0.6-2.9] p = 0.48
Foot examination performed	63 % [52/83]	61 % [49/80]	1.1 [0.6-2.0] p = 0.85	0.9 [0.5-1.8] p = 0.87
Eye examination performed	42 % [35/83]	43 % [34/80]	1.0 [0.5-1.8] p = 0.97	1.0 [0.5-2.0] p = 0.93
Influenza vaccine administered	29 % [24/83]	28 % [22/80]	1.1 [0.5-2.1] p = 0.84	1.1 [0.5-2.2] p = 0.84
Self-monitoring of blood glucose	54 % [45/83]	48 % [38/80]	1.3 [0.7-2.4] p = 0.39	1.3 [0.7-2.6] p = 0.45
Primary care encounters related to diabetes			1.0 [0.8-1.3] p = 0.85	1.0 [0.8-1.3] p = 0.90
	3 [6] [258]	3 [5] [243]		
Consultant encounters related to diabetes			0.9 [0.5-1.6] p = 0.79	1.0 [0.6-1.8] p = 0.96
	1 [1] [49]	1 [1] [51]		
Missed primary care appointments			0.9 [0.5- 1.4] p = 0.54	0.8 [0.5-1.3] p = 0.39
	1 [1] [43]	1 [1] [49]		
Total number of encounters and manoeuvres [assign 0 or 1 for binary indicators; exclude missed appointments]			1.0 [0.9-1.2] p = 0.74	1.0 [0.9 to 1.2] p = 0.85
	13 [42] [1106]	13 [38] [1039]		

Count indicators are reported as the mean number of measurements or encounters with the variance and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as rate ratio or odds ratio with the 95% confidence interval and p value.

Impact of free distribution of medicines in subgroup of people with hypertension

Among hypertension patients, free distribution was associated with less serum creatinine [aRR 0.6; 95 % CI 0.4-1.0; p=0.04] and electrolyte measuring (aRR 0.6; 95 % CI 0.4-1.0; p = 0.04) and fewer missed appointments (aRR 0.4; 95 % CI 0.2-0.9; p = 0.03) (see Table 3). There were trends towards fewer encounters with primary care providers (aRR 0.9; 0.7-1.1; p = 0.25) and consultants (aRR 0.6; 95 % CI 0.1-4.6; p = 0.61) but similar self-monitoring of blood pressure (aOR 1.1; 95 % CI 0.4-3.2; p = 0.86) (see Table 3). There was no difference in blood pressuring measuring in clinic. There were slightly more new medicine starts in participants receiving free distribution. Overall, the net change in the number of medicines prescribed to intervention participants was 15 new starts (a total of 20 new medicines started and 5 medicines stopped; average: 0.27 new medicines per person) and the net change for control participants was 0 (a total of 9 new medicines started and 9 medicines stopped).

Table 3. Hypertension process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
BP measurements	3 [4] [173]	3 [5] [160]	1.0 [0.7- 1.2] p = 0.67	1.00 [0.8-1.3] p = 0.92
Hemoglobin A1c measurements	1 [1] [37]	1 [1] [42]	0.8 [0.5- 1.2] p = 0.27	0.8 [0.5-1.3] p = 0.41
Lipid measurements	1 [1] [36]	1 [1] [37]	0.9 [0.5- 1.4] p = 0.49	0.9 [0.6-1.5] p = 0.70
Serum creatinine measurements	1 [4] [78]	2 [13] [110]	0.6 [0.4- 1.0] p = 0.05	0.6 [0.4 -1.0] p = 0.04
Serum electrolyte measurements	1 [3] [66]	2 [11] [103]	0.6 [0.3-0.9] p = 0.02	0.6 [0.4-1.0] p = 0.04
Primary care encounters	5 [9] [287]	6 [14] [302]	0.8 [0.7-1.1] p = 0.11	0.9 [0.7-1.1] p = 0.25
Consultant encounters related to hypertension	0 [0] [5]	0 [0] [5]	0.9 [0.1-6.1] p = 0.89	0.6 [0.1-4.6] p = 0.61
Missed primary care appointments	0 [0] [14]	0 [4] [44]	0.3 [0.1- 0.6] p = 0.00	0.4 [0.2-0.9] p = 0.03

Self-monitoring of blood pressure	21 % [12/56]	18 % [9/49]	1.2 [0.5-3.2] p = 0.70	1.1 [0.4-3.2] p = 0.86
Total number of encounters and manoeuvres [assign 0 or 1 for binary indicators; exclude missed appointments]	12 [43] [694]	16 [97] [768]	0.8 [0.6-1.0] p = 0.04	0.8 [0.7-1.0] p = 0.10

Count indicators are reported as the mean number of measurements or encounters with the variance and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as odds ratio or rate ratio with the 95% confidence interval and p value.

DISCUSSION

In this post-hoc analysis of randomized controlled trial findings, free distribution of medicines to people with diabetes or hypertension was not associated with more visits to primary care providers or consultants and, in fact, patients with hypertension had less laboratory monitoring and slightly fewer visits. Free distribution may slightly increase self-monitoring and reduce missed appointments.

The modest reductions in laboratory testing of serum creatinine and electrolytes for patients with hypertension may reflect appropriate clinical judgement against repeat testing. The Canadian guidelines recommend that the frequency of laboratory testing should be guided by clinical judgement and no specific intervals are mentioned in the guidelines. Clinicians may have been less likely to order laboratory testing in patients receiving free distribution because they had slightly better control of their blood pressure, possibly due to the greater number of medicines prescribed. These tests may also have been ordered less frequently because patients had fewer visits, potentially because they were self-monitoring. Systematic reviews have reported improved glycaemic control in diabetic patients performing self-monitoring of blood glucose, and reduced blood pressure in patients with hypertension self-measuring their blood pressure.[14,15] Thus, the observed trend towards more self-monitoring, if real, could reflect improved patient motivation, better disease control, or different guidance from clinicians. A 2018

1
2
3 randomized controlled trial found that using self-monitored blood pressure readings to titrate anti-
4 hypertensive treatments led to a significant reduction in blood pressure compared to the use of clinic
5 readings to guide care.[16] In this trial, patients with hypertension had a lower systolic blood pressure
6 after one year . The improvements in disease control and usefulness of self-measured blood pressure
7 readings may have resulted in clinicians asking patients to monitor their blood pressure at home rather
8 than attend clinic; this would explain both the increase in self-monitoring and the reduction in clinic
9 visits. A 1985 controlled trial of the effects of medical insurance on health spending and health status
10 reported lower blood pressure with free care, though the cause of the difference was additional contact
11 with physicians under free care. [17]
12
13
14
15
16
17
18
19
20
21
22
23

24 The reduction in missed appointments observed here may be explained by an improved clinician-patient
25 relationship and better perceived disease control. The reduction in missed appointments did not relate to
26 needing to attend appointments in order to get their free medications, as the study pharmacist had access
27 to their electronic medical record, could communicate with primary care providers, and medications were
28 mailed to participants. A 2004 study of patient perceptions found that emotional barriers [including the
29 fear of bad news] and perceived disrespect by the healthcare system caused patients to miss primary care
30 appointments.[18] Additionally, a 2014 cross-sectional survey reported that patients with hypertension
31 with no medication coverage and high medication costs were more likely to miss appointments.[19]
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

Patients may not take their medicines due to cost and may miss appointments due to feelings of
embarrassment or guilt over this; this may be obviated by free distribution of medicines.

Our study found that there was only a small non-significant increase in hemoglobin A1c monitoring and
serum creatinine monitoring in patients with diabetes. Our findings suggest that financial barriers to
medication access may not deter patients with diabetes from engaging in necessary health visits and
screening related to the management of their condition. In contrast, a study of American patients with
diabetes found that lower cost-related nonadherence was associated with improved compliance to annual

1
2
3 diabetes recommendations.[5] Financial incentives to clinicians, audit and feedback interventions, and
4 reminders to clinicians can achieve modest reductions in hemoglobin A1c, and our study found a small
5 increase in the frequency of HbA1c monitoring with free medicine distribution.[6]
6
7

8
9 The results of this study post-hoc analysis of trial findings suggest that improving access to chronic
10 disease medicines will not substantially increase costs associated with outpatient visits. To the contrary,
11 in this study free distribution appeared to increase self-monitoring, reduce visits for hypertension and
12 reduce the total number of healthcare encounters and manoeuvres performed in a year, without changing
13 the likelihood of visits for diabetes. Increasing access to medicines may encourage self-monitoring
14 practices, reduce in-person visits, and decrease laboratory investigations performed. Free distribution of
15 medicines may not only improve blood pressure control but could also reduce the per-person costs
16 associated with the management of hypertension.
17
18
19
20
21
22
23
24
25
26
27

28 Strengths of this study include the fact that the results are based on a randomized controlled trial.

29
30 Participants differed with respect to income level, ethnicity and location (urban versus rural). Despite the
31 fact that this was a post-hoc analysis and randomization was not stratified based on these characteristics,
32 we found that the groups were largely balanced; except for urban status. There are also some limitations
33 in this analysis. Associations identified during post-hoc analyses could be spurious and thus the findings
34 should be viewed as hypothesis-generating.[20] The study population is a subset of the CLEAN Meds
35 trial, and only included those with diabetes or hypertension based on whether they were prescribed at
36 least one diabetic or anti-hypertensive agent at the start of the trial; this reduced sample size is a
37 limitation. The trial was not designed to have sufficient power to detect differences in some of the
38 outcomes examined in this study so the failure to identify associations should be interpreted with caution.
39 Since the trial was unblinded, patients and clinicians could have been motivated by allocation to free
40 access to improve the process of care. The trial was conducted with primary care patients in a high-
41 income country who reported cost-related non-adherence and the findings may not apply in other settings.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The study was based on a review of primary care charts that do not reflect every actual encounter (e.g.
4 visits to other providers).
5
6
7
8

9 **CONCLUSION**

10
11 This post-hoc analysis of randomized controlled trial results found that free distribution of medicines may
12 improve self-monitoring behaviours and reduce missed primary care appointments for patients with
13 diabetes or hypertension. Free distribution may also reduce primary care and consultant appointments and
14 laboratory testing in patients with hypertension. Additionally, free distribution of medicines improves
15 disease control and improves patients' self-reported care. [21] Overall, these findings suggest that
16 improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate
17 health outcomes but also improves the patient experience and may also reduce healthcare costs by
18 encouraging self-monitoring practices. The hypotheses generated by this post-hoc analysis of randomized
19 controlled trial findings could be tested in future studies.
20
21
22
23
24
25
26
27
28
29
30
31

32 **FUNDING STATEMENT**

33
34 This work was supported by the Canadian Institutes of Health Research and the Keenan Research Summer
35 Student Program. They played no role in study design; in the collection, analysis and interpretation of data;
36 in the writing of the report; and in the decision to submit the article for publication.
37
38
39
40
41
42

43 **COMPETING INTERESTS STATEMENT**

44
45 NP reports grants from Canadian Institutes for Health Research, the Ontario SPOR Support Unit, the
46 Canada Research Chairs program and Physicians Services Incorporated during the conduct of the study.
47
48 All other authors (OC, HW, MA, BM and BS) declare that they have no competing interests.
49
50
51
52
53

54 **AUTHOR CONTRIBUTIONS**

1
2
3 OC contributed to the data curation, formal analysis, investigation, methodology, visualization, writing the
4 original draft and reviewing and editing. HW contributed to the data curation, formal analysis, investigation,
5 writing the original draft and reviewing and editing. MA contributed to the data curation, formal analysis,
6 and reviewing and editing. BM contributed to the methodology, validation, investigation, resources and
7 reviewing and editing. BS contributed to the methodology, validation, investigation, resources and
8 reviewing and editing. NP contributed to the conceptualization, methodology, validation, formal analysis,
9 investigation, resources, writing the original draft, reviewing and editing.
10
11
12
13
14
15
16
17
18
19

20 **DATA AVAILABILITY**

21
22 Deidentified participant data is available upon reasonable request from the corresponding author.
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] Braga M, Casanova A, Teoh H, Dawson KC, Gerstein HC, Fitchett DH, et al. Treatment gaps in the management of cardiovascular risk factors in patients with type 2 diabetes in Canada. *Can J Cardiol*. 2010 Jul;26[6]:297–302.
- [2] Saaddine JB, Engelgau MM, Beckles GL, Gregg EW, Thompson TJ, Narayan KMV. A Diabetes Report Card for the United States: Quality of Care in the 1990s. *Ann Intern Med*. 2002 Apr 16;136[8]:565.
- [3] Hajjar I, Kotchen TA. Trends in Prevalence, Awareness, Treatment, and Control of Hypertension in the United States, 1988-2000. *JAMA*. 2003 Jul 9;290[2]:199–206.
- [4] Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *Can Med Assoc J CMAJ Ott*. 2012 Feb 21;184[3]:297–302.
- [5] Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract*. 2018 Sep;143:24–33.
- [6] Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet Lond Engl*. 2012 Jun 16;379[9833]:2252–61.
- [7] Walsh JME, McDonald KM, Shojania KG, Sundaram V, Nayak S, Lewis R, et al. Quality improvement strategies for hypertension management: a systematic review. *Med Care*. 2006 Jul;44[7]:646–57.
- [8] Rosella LC, Lebenbaum M, Fitzpatrick T, O'Reilly D, Wang J, Booth GL, et al. Impact of diabetes on healthcare costs in a population-based cohort: a cost analysis. *Diabet Med J Br Diabet Assoc*. 2016 Mar;33[3]:395–403.
- [9] Weaver CG, Clement FM, Campbell NRC, James MT, Klarenbach SW, Hemmelgarn BR, et al. Healthcare Costs Attributable to Hypertension: Canadian Population-Based Cohort Study. *Hypertens Dallas Tex* 1979. 2015 Sep;66[3]:502–8.

- 1
2
3 [10] Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment
4 Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized
5 Clinical Trial. *JAMA Intern Med* [Internet]. 2019 Oct 7 [cited 2019 Oct 31]; Available from:
6 <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2752366>
7
- 8 [11] Diabetes Canada | Clinical Practice Guidelines - 2018 Full Guidelines [Internet]. [cited 2019 Sep
9 23]. Available from: <http://guidelines.diabetes.ca/cpg>
10
- 11 [12] Diagnosis & Assessment | Hypertension Canada Guidelines [Internet]. [cited 2019 Sep 23].
12 Available from: <https://guidelines.hypertension.ca/diagnosis-assessment/>
13
- 14 [13] Telus. PS Suite EMR.
15
- 16 [14] Zhu H, Zhu Y, Leung S. Is self-monitoring of blood glucose effective in improving glycaemic
17 control in type 2 diabetes without insulin treatment: a meta-analysis of randomised controlled trials.
18 *BMJ Open*. 2016 Sep 1;6[9]:e010524.
19
- 20 [15] Uhlig K, Patel K, Ip S, Kitsios GD, Balk EM. Self-measured blood pressure monitoring in the
21 management of hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2013 Aug
22 6;159[3]:185–94.
23
- 24 [16] McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J, et al. Efficacy of self-
25 monitored blood pressure, with or without telemonitoring, for titration of antihypertensive
26 medication [TASMINH4]: an unmasked randomised controlled trial. *The Lancet*. 2018 Mar
27 10;391[10124]:949–59.
28
- 29 [17] Keeler EB, Brook RH, Goldberg GA, Kamberg CJ, Newhouse JP. How Free Care Reduced
30 Hypertension in the Health Insurance Experiment. *JAMA*. 1985 Oct 11;254[14]:1926–31.
31
- 32 [18] Lacy NL, Paulman A, Reuter MD, Lovejoy B. Why We Don't Come: Patient Perceptions on No-
33 Shows. *Ann Fam Med*. 2004 Nov;2[6]:541–5.
34
- 35 [19] Nwabuo CC, Dy SM, Weeks K, Young JH. Factors associated with appointment non-adherence
36 among African-Americans with severe, poorly controlled hypertension. *PloS One*.
37 2014;9[8]:e103090.
38
- 39 [20] Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and
40 baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med*.
41 2002;21[19]:2917–30.
42
- 43 [21] Persaud N, Bedard M, Boozary A, Glazier RH, Gomes T, Hwang SW, et al. Effects of distributing
44 essential medications at no charge: results of a multicentre, unmasked, randomised controlled study.
45 *JAMA Intern Med*.
46
47
48
49
50
51
52
53
54
55
56
57
58
59

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

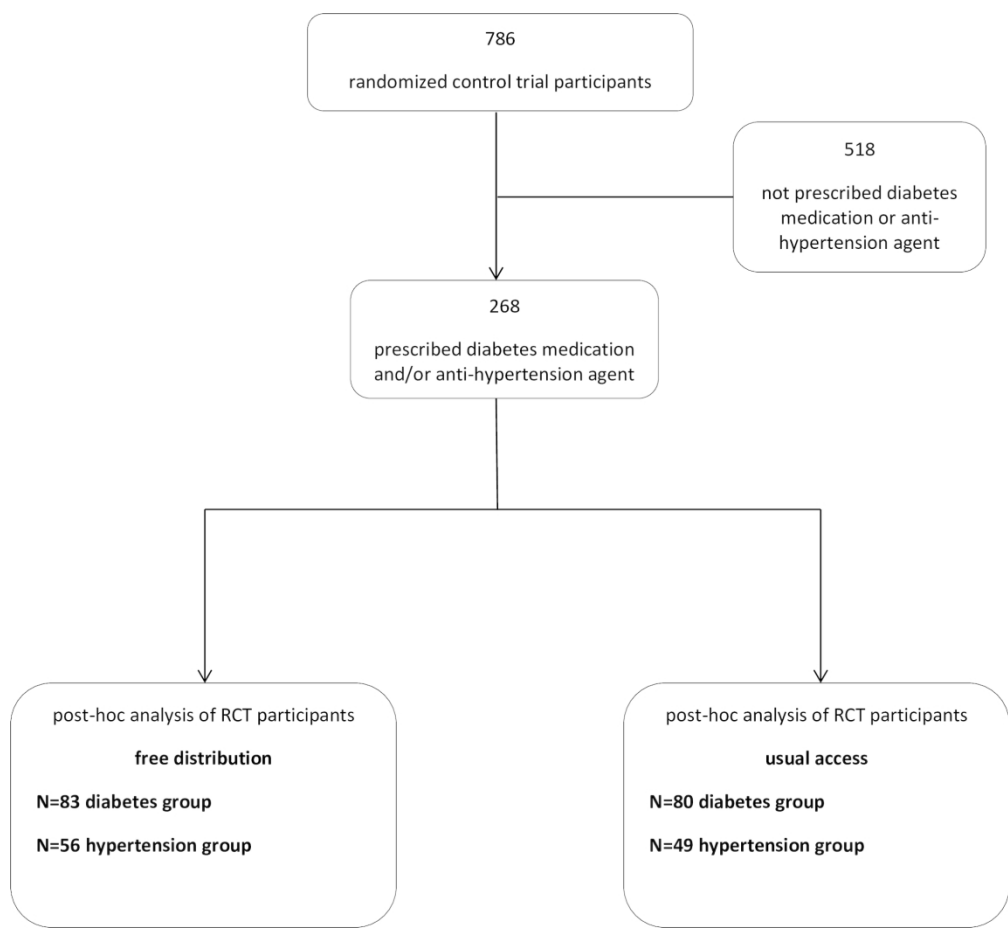


Figure 1. Flowchart illustrating study participant inclusion

190x173mm (300 x 300 DPI)

BMJ Open

Effect of free distribution of medicines on the process of care for adult patients with type 1 and type 2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042046.R2
Article Type:	Original research
Date Submitted by the Author:	02-Feb-2021
Complete List of Authors:	Charles, Onella; University of Toronto Faculty of Medicine; St Michael's Hospital Centre for Urban Health Solutions Woods, Hannah; St Michael's Hospital Centre for Urban Health Solutions Ally, Muhamad; St Michael's Hospital Centre for Urban Health Solutions Manns, Braden; University of Calgary Cumming School of Medicine, Department of Community Health Sciences ; University of Calgary Cumming School of Medicine, Department of Medicine Shah, Baiju; University of Toronto Institute of Health Policy Management and Evaluation; Institute for Clinical Evaluative Sciences Wang, Ri; St Michael's Hospital, MAP Centre for Urban Health Solutions Persaud, Nav; Unity Health Toronto, MAP Centre for Urban Health Solutions, St Michael's Hospital; University of Toronto
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health policy
Keywords:	DIABETES & ENDOCRINOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Effect of free distribution of medicines on the process of care for adult patients with type 1 and type**
4 **2 diabetes and hypertension: Post-hoc analysis of randomized control trial findings**
5

6 Onella Charles BSc^{1,2}, Hannah M Woods MSc², Muhamad Z Ally BSc², Braden Manns MD^{5, 6, 7, 8}, Baiju R
7 Shah MD^{3, 9, 10, 11}, Ri Wang², Nav Persaud MD^{2, 3, 4, 9}.
8

9 ¹ Faculty of Medicine, University of Toronto, 1 King's College Cir, Toronto, ON, Canada
10

11 ² MAP Centre for Urban Health Solutions, St. Michael's Hospital, 30 Bond St, Toronto, ON, Canada
12

13 ³ Department of Family and Community Medicine, University of Toronto, 500 University Ave, Toronto,
14 ON, Canada
15

16 ⁴ Department of Family and Community Medicine, St. Michael's Hospital, 80 Bond St, Toronto, ON,
17 Canada
18

19 ⁵ Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3330
20 Hospital Drive NW, Calgary, AB, Canada
21

22 ⁶ Department of Medicine, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW ,
23 Calgary, AB, Canada
24

25 ⁷ O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, 3280 Hospital
26 Dr NW, Calgary, AB, Canada
27

28 ⁸ Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive
29 NW, Calgary, AB, Canada
30

31 ⁹ Institute of Health Policy, Management, and Evaluation, University of Toronto, 155 College St, Toronto,
32 ON, Canada
33

34 ¹⁰ Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Toronto, ON, Canada
35

36 ¹¹ Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON,
37 Canada
38
39
40

41 **Corresponding author:** Nav Persaud, 80 Bond St. Toronto, Ontario, Canada M5B 1X2
42 Nav.persaud@utoronto.ca 416-864-6060 Ext 775778
43
44

45 **Key Words:** Essential medicine; diabetes; process of care; health outcome
46

47 **Wordcount:** 2981 **Figures:** 1 **Tables:** 3
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Objectives

The Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial randomized controlled trial showed that patients receiving free access to medicines had improved diabetes and hypertension outcomes compared to patients who had usual access to medicines. In this study, we aimed to test the impact of providing free access to medicine to people with diabetes and hypertension on process of care indicators.

Design

In this post hoc analysis of randomized controlled trial findings we identified process of care indicators for the management of diabetes and hypertension using relevant guidelines. The following process of care indicators were identified for diabetes management: encounters with healthcare professionals, blood pressure measurements, self-monitoring of blood glucose, annual eye and foot exam, annual administration of the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and urine albumin to creatinine ratio (ACR). We identified the following process of care indicators for hypertension: encounters with healthcare professionals, blood pressure measurements, self-measuring of blood pressure, and serum tests for electrolytes, HbA1c, lipids, and creatinine. Chart extractions were performed for all patients and the indicators for diabetes and hypertension were recorded. We compared the indicators for patients in each arm of the trial.

Results

The study included 268 primary care patients. Free distribution of medicines may improve self-monitoring behaviours (aRR 1.30; 95 % CI 0.66-2.57) and reduce missed primary care appointments for patients with diabetes (aRR 0.80; 95 % CI 0.48-1.33) or hypertension (aRR 0.41; 95 % CI 0.18-0.90). Free distribution may also reduce primary care and consultant appointments and laboratory testing in patients with hypertension.

Conclusions

1
2
3 Improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate
4 health outcomes but also improves the patient experience and may also reduce healthcare costs by
5 encouraging self-monitoring.
6
7
8
9

10 11 **STRENGTHS AND LIMITATIONS OF THIS STUDY** 12

- 13 • The study is based on a randomized controlled trial.
- 14 • Despite the fact that this was a post-hoc analysis and randomization was not stratified based on
15 these characteristics, we found that the groups were largely balanced.
- 16 • Associations identified during post-hoc analyses could be spurious and thus the findings should
17 be viewed as hypothesis-generating.
- 18 • The trial this study was based on was conducted with primary care patients in a high-income
19 country who reported cost-related non-adherence and the findings may not apply in other settings.
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

INTRODUCTION

Managing people with chronic diseases such as diabetes and hypertension with effective medicines and healthcare services can save lives and reduce complications, yet many people do not receive guideline-recommended care.[1–3] One important barrier to optimal care is cost related nonadherence which was reported by 9.6% of people who had received a prescription in the past year. [4] Cost related nonadherence could undermine the provision of healthcare services as people may avoid participating in care if they cannot afford prescribed medicines.[4,5]

Many strategies have been tested to improve the process of care for chronic diseases, with varying success. Resource intensive interventions such as financial incentives to providers and multidisciplinary changes to the primary care team are associated with modest improvements in diabetes and hypertension management.[6,7] Caring for patients with chronic diseases is expensive. [8] The cost and effectiveness of interventions to improve guideline-recommended care are important to consider, since increasing access to effective treatments may reduce costs related to complications, but may increase per-patient costs related to clinicians' monitoring of treatments and more expensive health technologies. [9]

We recently completed the Carefully Selected and Easily Accessible at No charge Medicines (CLEAN Meds) trial, a randomized controlled trial in which patients with self-reported cost-related medication nonadherence were randomly assigned to receive free distribution of medicines from a comprehensive list of essential medicines.[10] The CLEAN Meds trial found that providing Canadian primary care patients with medicines at no charge improved adherence to medication and, for patients with diabetes and hypertension, chronic disease management was improved based on some surrogate outcomes.[10] As previously reported, with free distribution of medicines, hemoglobin A1c levels were 0.4 % lower (95 % CI -0.76 to 0.0) compared with usual access, and systolic blood pressure was 7 mmHg lower (95% CI -11.7 to -2.8) compared with usual access.

1
2
3 We undertook this post-hoc analysis both to help understand why the intervention was beneficial in some
4 circumstances and why the intervention did not have a large benefit in general or any benefit for some
5 participants. Improving access to medicines could improve the process of care as patients who are
6 nonadherent may lack motivation for participating in care. Participation in diabetes education is
7 associated with both better quality of diabetes care and greater adherence to diabetes medicines,
8 indicating that medicine adherence and quality of care may improve together. [11] On the other hand,
9 improved adherence and better disease control could also lead to less participation in care. Patient-centred
10 medical homes is associated with improved quality of diabetes care but not with better medicine
11 adherence, suggesting that the process of care and medicine adherence can be uncoupled. [12] Given the
12 importance of medication related adherence in patients with chronic diseases, in this post-hoc analysis, we
13 tested the impact on diabetes and hypertension process of care indicators of providing free access to
14 medicine to people with diabetes and hypertension.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

35 **METHODS**

36 **Patients**

37 We identified patients in the CLEAN Meds trial with diabetes (with or without hypertension) or only
38 hypertension by identifying all participants prescribed at least one diabetic or anti-hypertensive agent at
39 the start of the trial. Randomization was not stratified based on these conditions. Because anti-
40 hypertensives such as ACE inhibitors and angiotensin receptor blockers are a standard part of diabetes
41 management (even when blood pressure is “normal”), we included patients who were prescribed both a
42 diabetic agent and an anti-hypertensive agent only in the diabetes group.
43
44
45
46
47
48
49
50
51
52
53

54 **Process of Care Indicators**

1
2
3 Using the care goals of diabetes and the Diabetes Canada Guidelines [13]) we identified the following
4 process of care indicators for the management of diabetes: encounters with healthcare professionals [in-
5 clinic appointments and telephone appointments with primary care physicians or nurse practitioners],
6 blood pressure measurements, self-monitoring of blood glucose, annual eye exam (with an optometrist or
7 ophthalmologist), foot screening exams (foot care and/or neuropathy screening), annual administration of
8 the influenza vaccine, and laboratory testing for hemoglobin A1c, LDL-cholesterol, serum creatinine, and
9 urine albumin to creatinine ratio (ACR).[13] Glycated hemoglobin (HbA1c) and self-monitoring blood
10 glucose (SMBG) can be used as indicators for the management of glycemic control.
11
12
13
14
15
16
17
18
19
20
21

22 Using the guidelines and the goals of care for hypertension and the Hypertension Canada Guidelines, [14]
23 we identified the following process of care indicators for the management of hypertension: encounters
24 with healthcare professionals, blood pressure measurements, self-measuring of blood pressure (at home or
25 at the pharmacy), and serum tests for electrolytes, HbA1c, lipids, and creatinine.
26
27
28
29
30
31
32

33 Since a number of the recommended clinical manoeuvres and other aspects of care (e.g. medicine
34 adjustments) involve patients interacting with healthcare providers, we also assess healthcare encounters
35 that included in person visits and telephone encounters with primary care physicians or nurse practitioners
36 where diabetes or hypertension were documented as being discussed.
37
38
39
40
41
42

43 **Data Collection**

44 Patients' primary care electronic medical records (EMRs) were accessed using the PS Suite software
45 (Telus Health) and information for the identified process of care indicators for diabetes and hypertension
46 were identified and abstracted. Two abstracters (OC, HW) were blinded to the patients' intervention
47 status at the time of chart abstraction. To ensure reliability of chart abstraction, each abstracter completed
48 5 chart abstractions independently and compared findings; there were no disagreements. OC, HW and
49 MA then completed the chart abstractions for all participants.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 For all patients with diabetes, starting from the patient's start date in the trial to one year later, the
6 following information was recorded from each chart: number of encounters with primary care physicians
7 and nurse practitioners related to diabetes (in-person visits and phone calls were included), number of
8 missed primary care appointments (this is tracked and missed appointments are explicitly stated in the
9 EMR), number of consultant (specialist physician) encounters related to diabetes, number of blood
10 pressure measurements performed at healthcare visits, number of serum hemoglobin A1c (HbA1c)
11 measurements, number of serum LDL-cholesterol (LDL-c) measurements, if serum creatinine (Cr) was
12 measured (binary; done during the year or not), if urine albumin to creatinine ratio (ACR) was measured
13 (binary), if the patient self-monitored their blood glucose levels (binary), if an annual eye screening exam
14 was performed (binary), if an annual foot screening exam was performed (binary), and if the annual
15 influenza vaccine was administered (binary). We also recorded the number of new diabetes medicines
16 each diabetic patient was prescribed and the number of diabetes medicines they stopped taking, during the
17 one year study period. All of this information was found in the charts as expected, however, flu vaccines
18 may have been given elsewhere, such as at a pharmacy, and may not have been fully captured in chart
19 review.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 For all patients with hypertension, starting from the patient's start date in the trial to one year later, the
42 following information was recorded: total number of encounters with primary care physicians and nurse
43 practitioners, number of consultant appointments related to hypertension, number of missed primary care
44 appointments, number of blood pressure measurements performed at healthcare visits; number of serum
45 electrolyte tests [any number of the following tests were included: Na, K, Cl, HCO₃⁻ and if a patient had
46 NA, K and Cl done on the same day, this was counted as one electrolyte test], number of serum HbA1c
47 measurements, number of serum lipid measurements (any number of the following tests were included:
48 LDL-c, HDL-c, non-HDL-c, triglycerides, cholesterol), number of serum creatinine (Cr) measurements,
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 if the patient self-measures their blood pressure either at home or at a community pharmacy (binary), and
4 the number of new hypertension medicines each patient was prescribed and stopped taking. This
5 information was found in the charts as expected.
6
7
8
9

10 11 **Data Analysis**

12 For clinical manoeuvres that are recommended to be performed multiple times during one year (e.g. blood
13 pressure measurements) and for encounters with healthcare professionals we report the rate ratios with
14 95% confidence intervals that were estimated using a negative binomial regression model. We report
15 unadjusted rate ratios and rate ratios adjusted for age, sex and clinic location (urban versus rural). We
16 compared the proportion of patients in each arm receiving clinical manoeuvres that are recommended to
17 be done only once during a one-year period (e.g. annual eye examination for people with diabetes) and
18 report the odds ratio with 95% confidence intervals that was estimated using a logistic regression model.
19 We report unadjusted odds ratios and odds ratios adjusted for age, sex and location (urban versus rural).
20 No p-value threshold was set for these post-hoc and hypothesis generating analyses.
21
22
23
24
25
26
27
28
29
30
31
32
33
34

35 We also compared the net change in medications for hypertension and diabetic patients in the intervention
36 and control arms. As part of the intervention, some patients had to switch medicines within a class. We
37 thus used net changes as a measure that would treat both groups similarly and captured whether or not
38 management had “intensified” by adding more agents.
39
40
41
42

43 **Patient and public involvement**

44 Patients or the public were not involved in the design, conduct, or reporting, or dissemination plans of our
45 research.
46
47
48
49
50

51 **RESULTS**

52 **Baseline characteristics**

53
54
55
56
57
58
59
60

Of the 786 patients enrolled in the CLEAN Meds trial, 163 patients were prescribed one or more medicines for diabetes and were included in the diabetes group [including 114 who were also prescribed one or more anti-hypertensive agents], and 105 patients were nondiabetic and prescribed one or more anti-hypertensive agents and included in the hypertension group. We thus included 268 participants in this study. Of the 163 patients with diabetes, 83 patients were in the intervention group receiving free distribution of medicines, while the remaining 80 patients were in the control group receiving standard access to medicines. Of the 105 patients with hypertension, 56 patients were in the intervention group receiving free distribution of medicines, and 49 patients were in the control group receiving standard access to medicines. Study participant inclusion is illustrated in Figure 1.

Figure 1. Flowchart illustrating study participant inclusion

For this posthoc analysis, the groups are balanced with the exception of hypertension in urban and rural groups. The characteristics of participants in the diabetes and hypertension groups are summarized in Table 1.

Table 1. Baseline participant characteristics.

	Diabetes [n = 163]		Hypertension [n = 105]	
	Free distribution Number [%] [n = 83]	Usual access Number [%] [n = 80]	Free distribution Number [%] [n = 56]	Usual access Number [%] [n = 49]
Women	35 [42.2]	35 [43.8]	22 [39.3]	17 [34.7]
Age [mean, SD]	59 ± 10	58 ± 11.2	60 ± 8.2	61 ± 9.3
Age 65 years or older	25 [30.1]	19 [23.8]	17 [30.4]	16 [32.7]
Ethnicity				
White	42 [50.6]	53 [66.3]	46 [82.1]	34 [69.4]
Black	9 [10.8]	10 [12.5]	2 [3.6]	4 [8.1]
Southeast or East Asian [incl Korean, Japanese, Filipino, Chinese]	6 [7.2]	2 [2.5]	4 [7.1]	2 [4.1]
South Asian	14 [16.9]	9 [11.3]	1 [1.8]	3 [6.1]
Latin American	1 [1.2]	3 [3.8]	0 [0.0]	2 [4.1]

West Asian [including Arab]	2 [2.4]	1 [1.3]	0 [0.0]	0 [0.0]
Mixed or other	9 [10.8]	2 [2.5]	2 [3.6]	4 [8.2]
Declined to provide	0 [0.0]	0 [0.0]	4 [7.1]	0 [0.0]
Main Income source				
Wages and salaries [including self-employed]	44 [53.0]	38 [47.5]	30 [53.6]	28 [57.1]
Pension	22 [26.5]	19 [23.8]	14 [25.0]	9 [18.4]
Social support [e.g. welfare or disability]	11 [13.3]	13 [16.3]	4 [7.1]	8 [16.3]
Unemployment insurance	4 [4.8]	3 [3.8]	4 [7.1]	2 [4.1]
Other	0 [0.0]	1 [1.3]	0 [0.0]	0 [0.0]
Declined to provide	2 [2.4]	6 [7.5]	4 [7.1]	2 [4.1]
Household income*				
\$30 000 CAD or less	46 [55.4]	41 [51.3]	23 [41.1]	19 [38.8]
\$30 000 to 70 000	24 [28.9]	22 [27.5]	12 [21.4]	12 [24.5]
\$70 000 or greater	3 [3.6]	4 [5.0]	4 [7.1]	0 [0.0]
Declined to provide	10 [12.0]	13 [16.3]	17 [30.4]	18 [36.7]
Number of medicines prescribed at baseline [mean, SD]	5 ± 2.8	5 ± 3.1	4 ± 2.0	4 ± 2.6
Urban site	50 [60.2]	48 [60.0]	22 [39.3]	27 [55.1]
Rural site	33 [39.8]	32 [40.0]	34 [60.7]	22 [44.9]

Impact of free distribution of medicines in subgroup of people with diabetes

For patients with diabetes, there were small increases in rates of serum creatinine measurement (aOR 1.33; 95 % CI 0.61-2.91; $p = 0.48$) but not hemoglobin A1c measurements (aRR 1.09; 95 % CI; 0.88-1.34; $p = 0.44$) for patients receiving free distribution compared to those with usual medicine access. There was a small increase self-monitoring of blood glucose (aRR 1.30; 95% CI 0.66 – 2.57; $p=0.45$) (see Table 2). There were no differences in appointments with primary care providers or consultants, but there was a trend toward fewer missed appointments with primary care providers (aRR 0.80; 95 % CI 0.48-1.33; $p = 0.39$) (see Table 2). There was no difference between the free distribution and usual access groups with respect to net change in medicine prescriptions. Overall, the net change in the number of medicines prescribed to participants receiving free distribution was 14 new starts (a total of 19 new medicines started and 5 medicines stopped; average of 0.17 new medicines per person) and the net change

for those with usual access was 14 new starts (a total of 21 new medicines started and 7 medicines stopped; average of 0.18 new medicines per person).

Table 2. Diabetes process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
Hemoglobin A1c measurements	2 [2] [187]	2 [2] [160]	1.13 [0.91-1.39] p = 0.27	1.09 [0.88-1.34] p = 0.44
BP measurements	3 [7] [278]	3 [7] [274]	0.98 [0.78-1.23] p = 0.85	0.96 [0.77-1.19] p = 0.71
LDL-c measurements	1 [1] [65]	1 [1] [61]	1.03 [0.72-1.46] p = 0.88	0.99 [0.70-1.41] p = 0.96
Urine ACR measured	54 % [45/83]	58 % [46/80]	0.88 [0.47-1.63] p = 0.67	0.88 [0.47-1.67] p = 0.70
Serum creatinine measured	82 % [68/83]	76 % [61/80]	1.41 [0.66- 3.02] p = 0.37	1.33 [0.61-2.91] p = 0.48
Foot examination performed	63% [52/83]	61% [49/80]	1.06 [0.56-2.00] p = 0.85	0.94 [0.49-1.84] p = 0.87
Eye examination performed	42 % [35/83]	43 % [34/80]	0.99 [0.53-1.84] p = 0.97	1.03 [0.53-2.01] p = 0.93
Influenza vaccine administered	29 % [24/83]	28 % [22/80]	1.07 [0.54-2.12] p = 0.84	1.08 [0.52-2.22] p = 0.84
Self-monitoring of blood glucose	54 % [45/83]	48 % [38/80]	1.31 [0.71-2.42] p = 0.39	1.30 [0.66-2.57] p = 0.45
Primary care encounters related to diabetes	3 [6] [258]	3 [5] [243]	1.02 [0.81-1.30] p = 0.85	1.02 [0.81-1.28] p = 0.90
Consultant encounters related to diabetes	1 [1] [49]	1 [1] [51]	0.93 [0.53-1.62] p = 0.79	1.01 [0.59-1.75] p = 0.96
Missed primary care appointments	1 [1] [43]	1 [1] [49]	0.85 [0.50- 1.44] p = 0.54	0.80 [0.48-1.33] p = 0.39
Total number of encounters and manoeuvres [assign 0 or 1 for	13 [42] [1106]	13 [38] [1039]	1.03 [0.88-1.19] p = 0.74	1.01 [0.88 to 1.17] p = 0.85

binary indicators; exclude missed appointments]				
---	--	--	--	--

Count indicators are reported as the mean number of measurements or encounters with the variance and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as rate ratio or odds ratio with the 95% confidence interval and p value.

Impact of free distribution of medicines in subgroup of people with hypertension

Among hypertension patients, free distribution was associated with a lower rate of serum creatinine [aRR 0.61; 95 % CI 0.38-0.97; p = 0.04] and electrolyte measuring (aRR 0.59; 95 % CI 0.36-0.98; p = 0.04), and fewer missed appointments (aRR 0.41; 95 % CI 0.18-0.90; p = 0.03) (see Table 3). There were trends towards fewer encounters with primary care providers (aRR 0.90; 0.71-1.10; p = 0.25) and consultants (aRR 0.59; 95 % CI 0.07-4.62; p = 0.61) but similar self-monitoring of blood pressure (aOR 1.10; 95 % CI 0.38-3.17; p = 0.86) (see Table 3). There was no difference in blood pressuring measuring in clinic. There were slightly more new medicine starts in participants receiving free distribution. Overall, the net change in the number of medicines prescribed to intervention participants was 15 new starts (a total of 20 new medicines started and 5 medicines stopped; average: 0.27 new medicines per person) and the net change for control participants was 0 (a total of 9 new medicines started and 9 medicines stopped).

Table 3. Hypertension process of care indicators.

	Free medicine distribution	Usual medicine access	Unadjusted difference	Adjusted difference
BP measurements	3 [4] [173]	3 [5] [160]	0.95 [0.74-1.22] p = 0.67	0.99 [0.77-1.27] p = 0.92
Hemoglobin A1c measurements	1 [1] [37]	1 [1] [42]	0.77 [0.49- 1.22] p = 0.27	0.83 [0.53-1.30] p = 0.41
Lipid measurements	1 [1] [36]	1 [1] [37]	0.85 [0.54- 1.35] p = 0.49	0.91 [0.57-1.46] p = 0.70

Serum creatinine measurements	1 [4] [78]	2 [13] [110]	0.62 [0.39- 1.00] p = 0.05	0.61 [0.38 -0.97] p = 0.04
Serum electrolyte measurements	1 [3] [66]	2 [11] [103]	0.56 [0.34-0.93] p = 0.02	0.59 [0.36-0.98] p = 0.04
Primary care encounters	5 [9] [287]	6 [14] [302]	0.83 [0.66-1.05] p = 0.11	0.9 [0.71-1.10] p = 0.25
Consultant encounters related to hypertension	0 [0] [5]	0 [0] [5]	0.88 [0.13-6.10] p = 0.89	0.59 [0.07-4.62] p = 0.61
Missed primary care appointments	0 [0] [14]	0 [4] [44]	0.28 [0.12- 0.64] p = 0.00	0.41 [0.18-0.90] p = 0.03
Self-monitoring of blood pressure	21 % [12/56]	18 % [9/49]	1.21 [0.46-3.18] p = 0.70	1.10 [0.38-3.17] p = 0.86
Total number of encounters and manoeuvres [assign 0 or 1 for binary indicators; exclude missed appointments]	12 [43] [694]	16 [97] [768]	0.79 [0.63-1.00] p = 0.04	0.83 [0.67-1.04] p = 0.10

Count indicators are reported as the mean number of measurements or encounters with the variance and the sum of all measurements or encounters. Binary indicators are reported as a proportion. Differences are adjusted for age, sex, and site and reported as odds ratio or rate ratio with the 95% confidence interval and p value.

DISCUSSION

In this post-hoc analysis of randomized controlled trial findings, free distribution of medicines to people with diabetes or hypertension was not associated with more visits to primary care providers or consultants and, in fact, patients with hypertension had less laboratory monitoring and slightly fewer visits. Free distribution may slightly increase self-monitoring and reduce missed appointments.

The modest reductions in laboratory testing of serum creatinine and electrolytes for patients with hypertension may reflect appropriate clinical judgement against repeat testing. The Canadian guidelines

1
2
3 recommend that the frequency of laboratory testing should be guided by clinical judgement and no
4 specific intervals are mentioned in the guidelines. Clinicians may have been less likely to order laboratory
5 testing in patients receiving free distribution because they had slightly better control of their blood
6 pressure, possibly due to the greater number of medicines prescribed. These tests may also have been
7 ordered less frequently because patients had fewer visits, potentially because they were self-monitoring.
8 Systematic reviews have reported improved glycaemic control in diabetic patients performing self-
9 monitoring of blood glucose, and reduced blood pressure in patients with hypertension self-measuring
10 their blood pressure.[15,16] Thus, the observed trend towards more self-monitoring, if real, could reflect
11 improved patient motivation, better disease control, or different guidance from clinicians. A 2018
12 randomized controlled trial found that using self-monitored blood pressure readings to titrate anti-
13 hypertensive treatments led to a significant reduction in blood pressure compared to the use of clinic
14 readings to guide care.[17] In this trial, patients with hypertension had a lower systolic blood pressure
15 after one year . The improvements in disease control and usefulness of self-measured blood pressure
16 readings may have resulted in clinicians asking patients to monitor their blood pressure at home rather
17 than attend clinic; this would explain both the increase in self-monitoring and the reduction in clinic
18 visits. A 1985 controlled trial of the effects of medical insurance on health spending and health status
19 reported lower blood pressure with free care, though the cause of the difference was additional contact
20 with physicians under free care. [18]

21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43 The reduction in missed appointments observed here may be explained by an improved clinician-patient
44 relationship and better perceived disease control. The reduction in missed appointments did not relate to
45 needing to attend appointments in order to get their free medications, as the study pharmacist had access
46 to their electronic medical record, could communicate with primary care providers, and medications were
47 mailed to participants. A 2004 study of patient perceptions found that emotional barriers [including the
48 fear of bad news] and perceived disrespect by the healthcare system caused patients to miss primary care
49 appointments.[19] Additionally, a 2014 cross-sectional survey reported that patients with hypertension
50
51
52
53
54
55
56
57
58
59
60

1
2
3 with no medication coverage and high medication costs were more likely to miss appointments.[20]

4
5 Patients may not take their medicines due to cost and may miss appointments due to feelings of
6
7 embarrassment or guilt over this; this may be obviated by free distribution of medicines.
8
9

10
11 Our study found that there was only a small non-significant increase in hemoglobin A1c monitoring and
12
13 serum creatinine monitoring in patients with diabetes. Our findings suggest that financial barriers to
14
15 medication access may not deter patients with diabetes from engaging in necessary health visits and
16
17 screening related to the management of their condition. In contrast, a study of American patients with
18
19 diabetes found that lower cost-related nonadherence was associated with improved compliance to annual
20
21 diabetes recommendations.[5] Financial incentives to clinicians, audit and feedback interventions, and
22
23 reminders to clinicians can achieve modest reductions in hemoglobin A1c, and our study found a small
24
25 increase in the frequency of HbA1c monitoring with free medicine distribution.[6]
26
27

28 The results of this study post-hoc analysis of trial findings suggest that improving access to chronic
29
30 disease medicines will not substantially increase costs associated with outpatient visits. To the contrary,
31
32 in this study free distribution appeared to increase self-monitoring, reduce visits for hypertension and
33
34 reduce the total number of healthcare encounters and manoeuvres performed in a year, without changing
35
36 the likelihood of visits for diabetes. Increasing access to medicines may encourage self-monitoring
37
38 practices, reduce in-person visits, and decrease laboratory investigations performed. Free distribution of
39
40 medicines may not only improve blood pressure control but could also reduce the per-person costs
41
42 associated with the management of hypertension.
43
44
45
46

47 Strengths of this study include the fact that the results are based on a randomized controlled trial.

48
49 Participants differed with respect to income level, ethnicity and location (urban versus rural). Despite the
50
51 fact that this was a post-hoc analysis and randomization was not stratified based on these characteristics,
52
53 we found that the groups were largely balanced; except for urban status. There are also some limitations
54
55 in this analysis. Associations identified during post-hoc analyses could be spurious and thus the findings
56
57
58
59

1
2
3 should be viewed as hypothesis-generating.[21] The study population is a subset of the CLEAN Meds
4 trial, and only included those with diabetes or hypertension based on whether they were prescribed at
5 least one diabetic or anti-hypertensive agent at the start of the trial; this reduced sample size is a
6 limitation. The trial was not designed to have sufficient power to detect differences in some of the
7 outcomes examined in this study so the failure to identify associations should be interpreted with caution.
8
9 We separated participants with diabetes from those with hypertension while we could have analysed some
10 shared outcomes (e.g. blood pressure measurement) using a single group with a larger sample size. Since
11 the trial was unblinded, patients and clinicians could have been motivated by allocation to free access to
12 improve the process of care. The trial was conducted with primary care patients in a high-income country
13 who reported cost-related non-adherence and the findings may not apply in other settings. The study was
14 based on a review of primary care charts that do not reflect every actual encounter (e.g. visits to other
15 providers).
16
17
18
19
20
21
22
23
24
25
26
27
28
29

30 **CONCLUSION**

31
32 This post-hoc analysis of randomized controlled trial results found that free distribution of medicines may
33 improve self-monitoring behaviours and reduce missed primary care appointments for patients with
34 diabetes or hypertension. Free distribution may also reduce primary care and consultant appointments and
35 laboratory testing in patients with hypertension. Additionally, free distribution of medicines improves
36 disease control and improves patients' self-reported care. [22] Overall, these findings suggest that
37 improving medicine accessibility for patients with diabetes and hypertension not only improves surrogate
38 health outcomes but also improves the patient experience and may also reduce healthcare costs by
39 encouraging self-monitoring practices. The hypotheses generated by this post-hoc analysis of randomized
40 controlled trial findings could be tested in future studies.
41
42
43
44
45
46
47
48
49
50
51
52

53 **FUNDING STATEMENT**

54
55
56
57
58
59
60

1
2
3 This work was supported by the Canadian Institutes of Health Research (grant number 381409) and the
4 Keenan Research Summer Student Program (award number 2019). They played no role in study design; in
5 the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit
6 the article for publication.
7
8
9
10

11 12 13 **COMPETING INTERESTS STATEMENT**

14
15 NP reports grants from Canadian Institutes for Health Research, the Ontario SPOR Support Unit, the
16 Canada Research Chairs program and Physicians Services Incorporated during the conduct of the study.
17
18 All other authors (OC, HW, MA, BM and BS) declare that they have no competing interests.
19
20
21
22
23

24 **AUTHOR CONTRIBUTIONS**

25
26 OC contributed to the data curation, formal analysis, investigation, methodology, visualization, writing the
27 original draft and reviewing and editing. HW contributed to the data curation, formal analysis, investigation,
28 writing the original draft and reviewing and editing. MA contributed to the data curation, formal analysis,
29 and reviewing and editing. BM contributed to the methodology, validation, investigation, resources and
30 reviewing and editing. BS contributed to the methodology, validation, investigation, resources and
31 reviewing and editing. RW contributed to methodology, formal analysis, investigation, and reviewing and
32 editing. NP contributed to the conceptualization, methodology, validation, formal analysis, investigation,
33 resources, writing the original draft, reviewing and editing.
34
35
36
37
38
39
40
41
42
43
44

45 **DATA AVAILABILITY**

46 Deidentified participant data is available upon reasonable request from the corresponding author.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Braga M, Casanova A, Teoh H, Dawson KC, Gerstein HC, Fitchett DH, et al. Treatment gaps in the management of cardiovascular risk factors in patients with type 2 diabetes in Canada. *Can J Cardiol*. 2010 Jul;26(6):297–302.
2. Saaddine JB, Engelgau MM, Beckles GL, Gregg EW, Thompson TJ, Narayan KMV. A Diabetes Report Card for the United States: Quality of Care in the 1990s. *Ann Intern Med*. 2002 Apr 16;136(8):565.
3. Hajjar I, Kotchen TA. Trends in Prevalence, Awareness, Treatment, and Control of Hypertension in the United States, 1988-2000. *JAMA*. 2003 Jul 9;290(2):199–206.
4. Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *Can Med Assoc J CMAJ Ott*. 2012 Feb 21;184(3):297–302.
5. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract*. 2018 Sep;143:24–33.
6. Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet Lond Engl*. 2012 Jun 16;379(9833):2252–61.
7. Walsh JME, McDonald KM, Shojania KG, Sundaram V, Nayak S, Lewis R, et al. Quality improvement strategies for hypertension management: a systematic review. *Med Care*. 2006 Jul;44(7):646–57.
8. Rosella LC, Lebenbaum M, Fitzpatrick T, O'Reilly D, Wang J, Booth GL, et al. Impact of diabetes on healthcare costs in a population-based cohort: a cost analysis. *Diabet Med J Br Diabet Assoc*. 2016 Mar;33(3):395–403.
9. Weaver CG, Clement FM, Campbell NRC, James MT, Klarenbach SW, Hemmelgarn BR, et al. Healthcare Costs Attributable to Hypertension: Canadian Population-Based Cohort Study. *Hypertens Dallas Tex 1979*. 2015 Sep;66(3):502–8.
10. Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial. *JAMA Intern Med [Internet]*. 2019 Oct 7 [cited 2019 Oct 31]; Available from: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2752366>
11. Murray CM, Shah BR. Diabetes self-management education improves medication utilization and retinopathy screening in the elderly. *Prim Care Diabetes*. 2016;10(3):179–85.

12. JaeJin A. The Impact of Patient-Centered Medical Homes on Quality of Care and Medication Adherence in Patients with Diabetes Mellitus. *Journal of Managed Care and Specialty Pharmacy*. 2016 Nov 22;22(11):1272–84.
13. Diabetes Canada | Clinical Practice Guidelines - 2018 Full Guidelines [Internet]. [cited 2019 Sep 23]. Available from: <http://guidelines.diabetes.ca/cpg>
14. Diagnosis & Assessment | Hypertension Canada Guidelines [Internet]. [cited 2019 Sep 23]. Available from: <https://guidelines.hypertension.ca/diagnosis-assessment/>
15. Zhu H, Zhu Y, Leung S. Is self-monitoring of blood glucose effective in improving glycaemic control in type 2 diabetes without insulin treatment: a meta-analysis of randomised controlled trials. *BMJ Open*. 2016 Sep 1;6(9):e010524.
16. Uhlig K, Patel K, Ip S, Kitsios GD, Balk EM. Self-measured blood pressure monitoring in the management of hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2013 Aug 6;159(3):185–94.
17. McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *The Lancet*. 2018 Mar 10;391(10124):949–59.
18. Keeler EB, Brook RH, Goldberg GA, Kamberg CJ, Newhouse JP. How Free Care Reduced Hypertension in the Health Insurance Experiment. *JAMA*. 1985 Oct 11;254(14):1926–31.
19. Lacy NL, Paulman A, Reuter MD, Lovejoy B. Why We Don't Come: Patient Perceptions on No-Shows. *Ann Fam Med*. 2004 Nov;2(6):541–5.
20. Nwabuo CC, Dy SM, Weeks K, Young JH. Factors associated with appointment non-adherence among African-Americans with severe, poorly controlled hypertension. *PloS One*. 2014;9(8):e103090.
21. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med*. 2002;21(19):2917–30.
22. Persaud N, Bedard M, Boozary A, Glazier RH, Gomes T, Hwang SW, et al. Effects of distributing essential medications at no charge: results of a multicentre, unmasked, randomised controlled study. *JAMA Intern Med*.

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

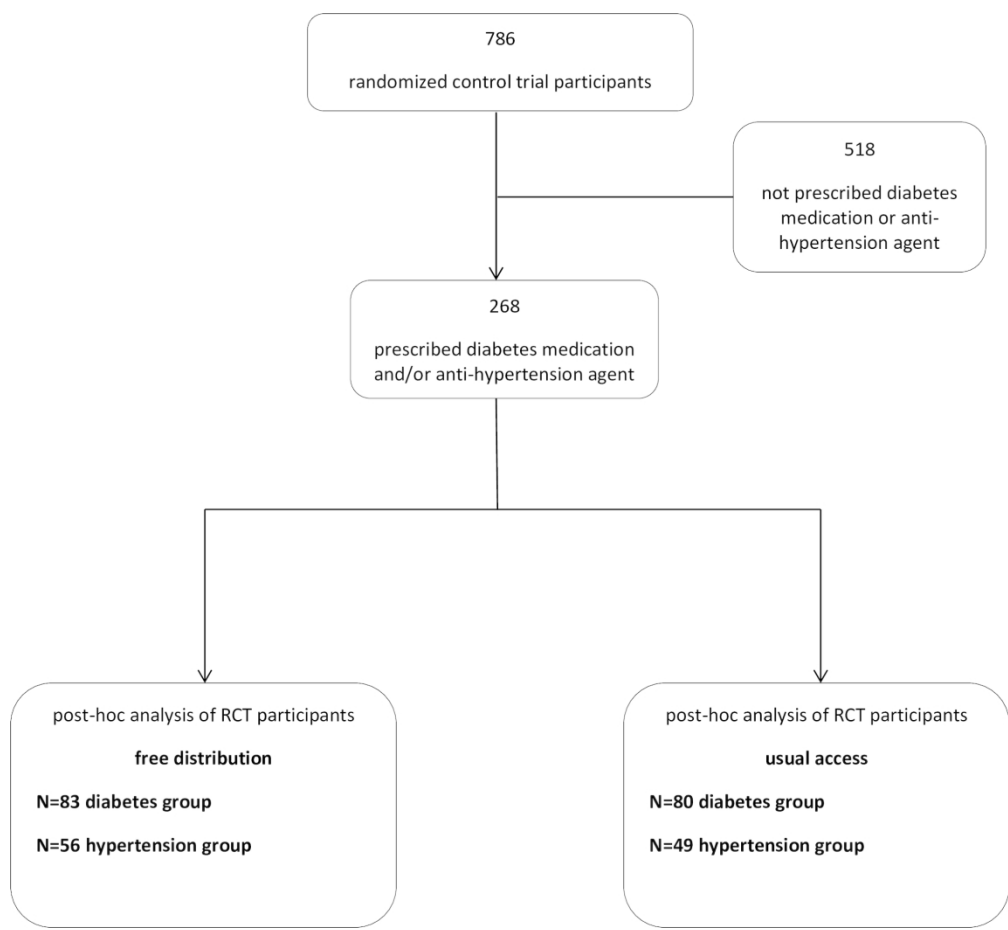


Figure 1. Flowchart illustrating study participant inclusion

190x173mm (300 x 300 DPI)