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Authors

Iyer, Priyanka
Gao, Yubo
Jalal, Diana
et al.

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ORIGINAL ARTICLE

Hydroxychloroquine use is associated with reduced mortality risk in older adults with rheumatoid arthritis

Priyanka Iyer[1] · Yubo Gao[2] · Diana Jalal[3] · Saket Girotra[4] · Namrata Singh[5] · Mary Vaughan-Sarrazin[6]

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Abstract

Background There is little robust data about the cardiovascular safety of hydroxychloroquine in patients with rheumatoid arthritis (RA), who often have cardiovascular comorbidities. We examined the association between use of hydroxychloroquine (HCQ) in patients with RA and major adverse cardiovascular events (MACE).

Methods In a retrospective cohort of Medicare beneficiaries aged ≥ 65 years with RA, we identified patients who initiated HCQ (users) and who did not initiate HCQ (non-users) between January 2015-June 2017. Each HCQ user was matched to 2 non-users of HCQ using propensity score derived from patient baseline characteristics. The primary outcome was the occurrence of MACE, defined as acute admissions for stroke, myocardial infarction, or heart failure. Secondary outcomes included all-cause mortality and the composite of MACE and all-cause mortality. Cox proportional hazards model was used to compare outcomes between HCQ users to non-users.

Results The study included 2380 RA patients with incident HCQ use and matched 4633 HCQ non-users over the study period. The mean follow-up duration was 1.67 and 1.63 years in HCQ non-users and users, respectively. In multivariable models, use of HCQ was not associated with the risk of MACE (hazard ratio 1.1; 95% CI: 0.832–1.33). However, use of HCQ was associated with a lower risk of all-cause mortality (HR: 0.54; 95% CI: 0.45–0.64) and the composite of all-cause mortality and MACE (HR 0.67; 95% CI: 0.58–0.78).

Conclusion HCQ use was independently associated with a lower risk of mortality in older adults with RA but not with incidence of MACE events.

Key Points

- *Using an incident user design (to avoid the biases of a prevalent user design) and a population-based approach, we examined the effect of hydroxychloroquine (HCQ) on the risk of major cardiovascular events (MACE) in older patients with RA.*
- *We did not find an association between HCQ use and incident MACE. We did, however, find a significant association with the composite outcome (MACE and all-cause mortality) driven by a significant reduction in all-cause mortality with HCQ use.*

Keywords Cardiovascular events · Hydroxychloroquine · MACE · Rheumatoid arthritis

Introduction

Despite advances in preventative medicine for atherosclerotic cardiovascular disease (CVD) (cardiac death, stroke, acute coronary syndrome, and heart failure), CVD continues to be a major cause of morbidity and mortality in the elderly, indicating an urgent need for novel therapies [1, 2]. Cardiovascular (CV) events occur more frequently than expected in patients with rheumatoid arthritis (RA) due to subclinical atherosclerosis [3] that may develop even before the diagnosis of RA. In addition, plaques are more inflamed and rupture-prone [4]. This increased incidence is not entirely explained by traditional CV risk factors [5] and the magnitude of excess risk is similar to that reported for patients with diabetes mellitus [6].

Hydroxychloroquine is a well-known immunomodulatory medication widely used in the treatment of several rheumatic diseases, including RA and systemic lupus erythematosus (SLE). Moreover, it has been postulated to have several mechanisms of cardioprotective effect, including a decreased

Namrata Singh and Mary Vaughan-Sarrazin are co-senior authors.

✉ Namrata Singh
nasingh@uw.edu

Extended author information available on the last page of the article

risk of incident diabetes [7], improved insulin resistance [8], better lipid profile [9], and anti-platelet properties [10]. Research highlighting the potential extra-articular benefits of hydroxychloroquine in RA is lagging. Given the increasing prevalence of RA and CVD in the elderly, it is important to study the effect of HCQ, a relatively inexpensive and safe medication, on cardiovascular outcomes [11, 12]. Investigation of the potential association between the use of HCQ and cardiovascular outcomes in the elderly is critically important since 2/3 of patients with cardiovascular disease in the U.S. are adults 65 years and older [13].

Our objective was to assess whether HCQ use was independently associated with a reduction in the risk of major adverse cardiovascular events (MACE), defined as acute admissions for ischemic stroke, myocardial infarction, or heart failure, in adults 65 years and older with RA using a population-based approach. We also evaluated the relationship between HCQ use and the risk of death, and the composite of death, or MACE.

Methods

Data sources and patient selection

A retrospective cohort study was conducted using claims incurred during 2014–2017 for Medicare beneficiaries included in the Medicare 5% enhanced random sample. Data was acquired from the Centers for Medicare and Medicaid Services (CMS). The cohort included beneficiaries aged 65 years and older with inpatient or outpatient encounters for RA during January 2015-June 2017, as identified in Medicare Part A and Part B claims. Patients with RA were identified based on International Classification of Diseases, Ninth and Tenth Revision (ICD) diagnosis codes – 714.0, 714.2, M05.xx and M06.xx, excluding M06.4 and M06.1. Beneficiaries were required to have at least two RA-related codes 90 days apart after January 2015 to qualify. The Institutional Review Board at the University of Iowa approved the study and waived the need for patient informed consent for this database study due to the large cohort size and the use of routinely collected billing data.

Patients who initiated HCQ from January 2015 through June 2017 were identified in Medicare Part D claims. The index date for HCQ users was defined as the date of the patient's first pharmacy claim for HCQ. To ensure complete availability of claims for assessing patient comorbidities and HCQ use, patients were excluded if they were not continuously enrolled in Medicare Parts A, B, and D for 12 months before the Index Date, had HCQ use prior to 2015, were enrolled in a Medicare Advantage plan during the 12 months before the index date, stayed in a nursing home during the preceding 12 months, or were placed on palliative status during the 12 months before the index date.

Potential controls (i.e., non-HCQ users) were identified among patients with RA who did not initiate HCQ during the observation period and had no use of HCQ prior to 2015. Because HCQ users may initiate HCQ at any time during the observation period, we defined multiple possible index dates for each potential control patient. The first possible index date was defined as the date of the second RA encounter (since all eligible patients were required to have two RA encounters within 90 days). A new potential index date was assigned each quarter thereafter. The same exclusion criteria used to identify new HCQ users were applied to each index date for potential control patients (i.e., potential index dates for control patients were excluded if they were not continuously enrolled in Medicare Parts A, B, and D for 12 months, had prior use of HCQ, were enrolled in Medicare managed care, stayed in a nursing home, or were on palliative status during the 12 months before the potential index date).

Study outcomes

Our primary outcome of interest was MACE, defined as the first hospitalization for ischemic stroke, myocardial infarction, or heart failure after the index date. The definition of major acute cardiovascular event (MACE) varies in the literature. In our study, we defined MACE as hospitalizations with primary diagnosis of acute myocardial infarction, ischemic stroke, or heart failure, consistent with other studies [14–17] (Supplemental Table 1). Prior studies validating case definitions of acute MI [18], ischemic stroke [19], or acute heart failure hospitalizations [20] using ICD codes have shown high positive predictive values or sensitivity, as compared to medical records. Positive predictive value for acute ischemic stroke, acute myocardial infarction, and acute heart failure hospitalizations are reported as 0.82 [18], 0.92 [19], and 0.98 [20], when the ICD code is listed in the principal diagnosis position.

Secondary outcome measures included all-cause mortality, and a composite of MACE and all-cause mortality. Follow-up started at the index date and continued until the first MACE, the end of HCQ use (defined as a gap of > 90 days from the last fill), or the end of the observation period (December 31, 2017).

Covariates and statistical analysis

To facilitate valid comparisons, each case was matched to two control patients based on patient characteristics as of the index date, as reflected in propensity scores. Specifically, each HCQ user ("case") was matched with two patients who did not initiate HCQ ("control") during the same year and

quarter as the index date and had similar characteristics at the time based on the time-specific propensity scores.

We used multivariable logistic regression models to estimate the propensity for initiating HCQ for each patient and index date. Specific patient characteristics included in propensity models were identified for each possible index date for each patient and included demographics, comorbidities, other medication use (cardioprotective agents, non-steroidal anti-inflammatory drugs [NSAIDs], opioids, steroids, biologic DMARDs (etanercept, adalimumab, infliximab, abatacept, anakinra, certolizumab, golimumab, rituximab, tocilizumab, tofacitinib), non-biologic DMARDs (methotrexate, leflunomide, minocycline, sulfasalazine) and prior inpatient hospital days. Patient demographics (age, sex, and race) were obtained from the Medicare Beneficiary Summary file; comorbidities were defined based on previously published algorithms [21] and identified using claims incurred during the 12 months prior to index dates; other medication use was defined from Part D claims incurred during the 90 days prior to the index date. Subsequently, each patient who initiated HCQ was matched to two similar patients who did not initiate HCQ, using nearest neighbor matching with a caliper of 0.25 times the standard deviation of the propensity score logit. To ensure similar follow-up times for HCQ-users and non-users, propensity matching occurred within the quarter, as defined by index dates. Although each HCQ non-user had multiple possible index dates, each non-user was selected only once in the matching algorithm. Characteristics of matched samples were compared to ensure adequate balance, which we defined as standardized differences < 10% [22].

Finally, we compared incident MACE, all-cause mortality, and the composite outcome between HCQ users and non-users in the matched cohort using Kaplan–Meier analysis. Additionally, Cox proportional hazard regression models in the matched cohort were used to calculate the hazard ratio (HR; and 95% CI) of each outcome for matched HCQ user relative to non-user.

Results

Study population characteristics

We identified 33,425 unique patients aged 65 years and older with 2 or more RA encounters between 1/1/2015 and 06/30/2017. Of these, 7,491 were excluded due to HCQ use prior to 2015. After excluding HCQ users and potential controls that were not continuously enrolled in Medicare Parts A, B, and D, were enrolled in a Medicare Advantage plan, or stayed in a nursing home or palliative care during the 12 months before the index date, the remaining sample included 14,924 patients, of whom 2,447 initiated HCQ during 2015-June 2017. The final sample included 2380 HCQ users that were matched with 4633 non-users (2:1 match) after propensity matching (Fig. 1). The mean (± SD) age in both groups was around 74 (± 6.3) years, with a predominantly female population. Standardized differences in characteristics between patients taking HCQ and not taking HCQ in the matched sample were less than 10% (Table 1). In addition, the mean follow-up time was similar for patients taking HCQ and patients not taking HCQ (1.63 years versus 1.67 years).

HCQ use and the risk of MACE and death

During the observation period, 307 MACE events occurred in the matched sample, including 111 in HCQ users (2.8 per 100 patient-years) and 196 in the non-user group (incidence rate of 2.6 per 100 patient-years). Using Cox regression, there were no differences in the hazard of MACE for patients who initiated HCQ, relative to non-users (1.1 (95% CI: 0.832–1.327) (Table 2). In contrast, we observed a 46% reduction in all-cause mortality (HR = 0.54; (95% CI: 0.45–64), and a 33% reduction in the composite outcome (HR = 0.67; 95% CI, 0.48–0.78) among HCQ users compared to non-users.

Discussion

Using an incident user design (to avoid the biases of a prevalent user design) and a population-based approach, we examined the effect of HCQ on the risk of MACE in elderly patients with RA. We matched HCQ users and non-users to understand whether the association of HCQ was independent of other CAD risk factors and treatments. Contrary to our hypothesis, we found no association between HCQ use and MACE. We did, however, find a significant association with the composite outcome driven by a significant reduction in all-cause mortality with HCQ use.

Several studies have examined the potential association between HCQ and cardiovascular outcomes, with conflicting results [23–34]. The majority of these studies have been conducted on patients with SLE, and only a few have focused on patients with RA. A study from the Netherlands examined the effect of different combinations of DMARDs on CVD in RA and did not find a protective effect for HCQ alone, odds ratio (OR) for CVD with HCQ use alone was 0.45 (95% CI 0.1 – 2.04) showing no significant association between HCQ use and the development of CVD after correction for age, gender, smoking, RA duration, hypertension, diabetes, and hypercholesterolemia [24]. In a systematic review and meta-analysis, Liu et al. reported no association in CVD risk with chloroquine (CQ)/HCQ use based on limited studies in RA (RR 0.81, 95% CI 0.46–1.41) [35]. In contrast, researchers from the US found that HCQ use was associated with a 72%

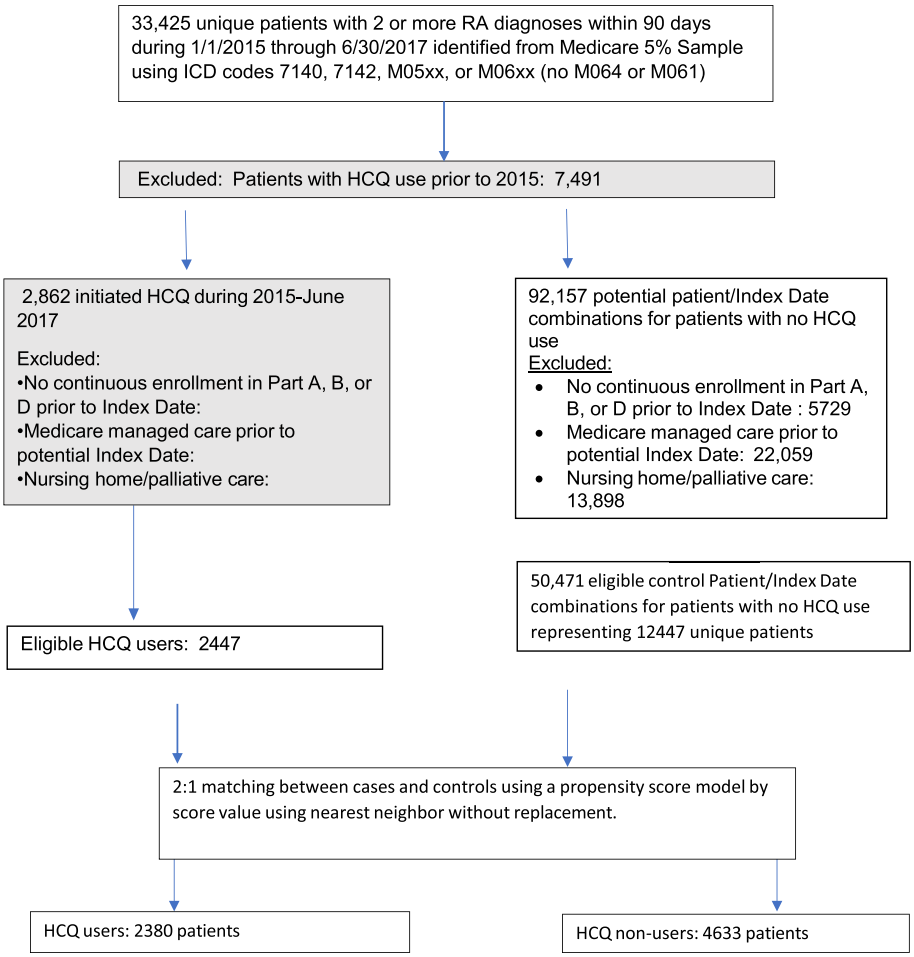

Fig. 1 Flow-chart showing cohort selection process

decrease in the risk of incident CVD in RA patients [25]. However, in this retrospective cohort study from a single health system, patients had a mean age of 56.3 years. It is plausible that the older age of our population has contributed to the differential results. A large systematic review and meta-analysis with 12245 HCQ users with RA showed that HCQ may lower the incidence of diabetes, facilitate improvement in lipid profiles, and, to a lesser extent, lower the risk of cardiovascular events and insulin resistance [36]. According to a case–control study by Jorge et al., people with RA and SLE who currently utilize HCQ tended to have a lower risk of MI (OR 0.88 [0.74- 1.05)] and stroke (0.87 [0.74—1.03)) and the authors concluded that there was a decrease in overall CV events with current HCQ use [37]. A study by D'Andrea and group compared individuals who initiated hydroxychloroquine to those who started taking methotrexate using propensity score matching with 54,462 RA patients aged > 65 in the Medicare population and studied the development of sudden cardiac arrest or ventricular arrythmia (SCA/VA); and 2) 3-point major adverse cardiovascular event (MACE) (i.e., a hospitalization for acute myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular mortality) [38]. In comparison to methotrexate, hydroxychloroquine did not increase the incidence of SCA/VA (HR: 1.03; 95% CI: 0.79–1.35) or MACE (HR: 1.07; 95% CI: 0.97–1.18). Incident hydroxychloroquine use in patients with a history of HF was associated with an increased risk of MACE compared to methotrexate.

A significant finding of our analysis is that incident HCQ use in the older adult population with RA is associated with reduced mortality. These findings are similar to results from a Danish study that observed a significant reduction in all-cause mortality and cardiovascular related death among HCQ initiators, with a hazard ratio of 0.83 (95% confidence interval [CI] 0.71–0.97) and 0.78 (95% CI: 0.61 to 0.99), respectively [39]. Similar to our results, no association was observed between HCQ use and ischemic events (MI or stroke). These results contrast with the report by Faselis et al. [40], who observed that HCQ use was not associated with a lower risk of all-cause mortality 12 months after HCQ initiation for RA [40]. However, there are significant differences between their study and ours. First, their study population is predominantly male in contrast to ours, which is predominantly female (14% versus 74%). Second,

Table 1 Demographic characteristics of HCQ users and non-users after matching

Characteristics, n(%)	RA HCQ users ($n=2380$)	RA HCQ non-users ($n=4633$)	Standardized difference (after matching)
Demographics			
Age, mean (± SD)	74.1(6.3)	74.3 (6.2)	-0.08
Female sex, %(N)	75.3% (1785)	73.0% (3382)	-0.02
Race/ethnicity			
White	81.09% (1930)	80.28% (3700)	0.02
Black	8.2% (190)	9.0% (417)	-0.01
Hispanic	5.8% (121)	6.9% (324)	-0.02
Other	1.9% (47)	4.5% (208)	-0.01
Baseline comorbidities			
Hypertension	76.0% (1809)	78.6% (3642)	-0.06
Diabetes mellitus	31.7% (754)	34.0% (1577)	-0.04
Smoking	12.2% (291)	13.2% (611)	-0.02
Prior coronary revascularization	6.1% (145)	6.4% (297)	-0.01
Prior heart failure	11.8% (281)	14.0% (648)	-0.03
Prior myocardial infarction	3.9% (93)	4.1% (192)	-0.06
Prior CAD	25.8% (614)	27% (1249)	-0.02
Prior ischemic stroke	10.6% (251)	11.2% (520)	-0.01
Medications used in prior 90 days			
Steroids	63.1% (1504)	60.4% (2798)	0.07
Biologic DMARDs	29.5% (707)	27.2% (1280)	0.04
Methotrexate	26.8% (637)	24.8% (1148)	0.04
Other non-biologic DMARDs	(18.4%) 442	17.9 (841)	0.03
TNFi	3.28% (78)	4.34% (201)	-0.05
NSAIDs	42.5% (1011)	40.9% (1895)	0.03
Opioids	42.0% (1000)	45.3% (2100)	-0.06
Statins	44.3% (1054)	47.5% (2200)	-0.06

Abbreviations: *CAD* Coronary artery disease; *DMARDs* disease modifying anti-rheumatic agents; *MI* myocardial infarction; *NSAIDs*, Non-steroidal anti-inflammatory drugs; *TNFi* Tumor necrosis factor inhibitor

Table 2 Association between hydroxychloroquine use and cardiovascular outcomes and death based on multivariable models

Number of events (rate per 100 patient-years) and Relative hazard from Cox proportional hazard models on matched sample				
Characteristic	HCQ nonusers ($n=4633$)	HCQ($n=2380$)	Relative hazard (95% CI)	p value
Primary outcome: MACE	196 (2.6)	111 (2.8)	1.05 (0.83–1.33)	0.68
Death	519 (6.8)	150 (3.6)	0.54 (0.45–0.64)	< 0.001
Composite	646 (8.7)	234 (5.8)	0.67 (0.58–0.78)	< .0.001

HCQ Hydroxychloroquine; *MACE* Major adverse cardiovascular events

our study population is older and therefore likely at higher risk of death (mean age 63.9 years versus 74 years).

HCQ has been found to reduce mortality in patients with SLE [41, 42]. A recent study from Canada found a nearly four-fold increased risk of death associated with recent HCQ discontinuation [43]. They also demonstrated a 65% reduced risk of death among current HCQ users compared with remote users (> 365 days), suggesting a potential benefit of current HCQ use and a consequent decrease in all-cause mortality. Antimalarials, according to Shinjo et al., have a protective effect against thromboses in lupus patients, increasing survival rates [42]. The use of hydroxychloroquine remained highly protective for thrombosis in a large and ethnically diverse SLE US cohort after disease severity and propensity scores were adjusted for (OR 0.62, $p=4.91\times10^{-4}$) [44]. Although we are unable to ascertain the causes of death in the Medicare database, based on the above literature, we hypothesize that the survival benefit seen among HCQ users in RA might be in part related to non-MACE events (e.g., protection against fatal

thrombotic events such as pulmonary embolism) or possibly decreased mortality from sepsis.

For the treatment of RA, biologic and conventional DMARDs are often prescribed together, making the analysis complicated. We tried to minimize confounding by using propensity score matching by age, gender, comorbidities, statins, glucocorticoids, methotrexate, biologics, and NSAIDs, and a multivariable regression model that adjusted for relevant confounders. We used an incident user design and a population-based approach to examine the effect of HCQ on the risk of CVD in the U.S. elderly.

Our study also has several limitations. Because we used Medicare data, there was no information available on disease activity of RA or on the degree of systemic inflammation (such as C-reactive protein, erythrocyte sedimentation rate), which may have an impact on the risk of CVD. Additionally, our data sources were limited to the period between 2014–2017, and thus we had a short follow-up. Therefore, our results preclude the conclusion that use of HCQ exerts a cardioprotective effect among elderly patients with RA over a longer period of time. The number of MACE events may have been too low to detect the statistical significance of findings in certain subgroups, i.e., type II error; the availability of an even larger sample size would likely have overcome this limitation. Our study looked at the association between HCQ use and MACE and mortality among older adults with RA and so, the results cannot be generalizable to younger patients with RA. But older adults are among the high-risk group for the occurrence of MACE and mortality and so, the results of this study can be informative for counseling them. Another major limitation of the study was the lack of other factors that may influence the risk of CVD, including body mass index and lifestyle preferences (cigarette use, aspirin use, impact of exercise, underlying renal disease and family history of cardiovascular disease). The diagnosis of RA, CAD, and medical comorbidities was based solely on the ICD codes from the Medicare database, not from medical chart review. Thus, misclassification bias cannot be completely excluded. A key limitation of analyses using observational data is the potential for non-random treatment assignment to introduce selection bias, leading to biased conclusions. While we used a sophisticated algorithm to match patients with and without HCQ use, this approach controlled for observed patient characteristics only.

Conclusions

In conclusion, we found that HCQ use was independently associated with a lower risk of mortality in older adults with RA. Besides replication in future studies, there is a need to explore factors that mediate this potentially protective effect and assess whether these factors are dependent or independent of HCQ serum levels.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-023-06714-5.

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Declarations

Disclosures None.

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Authors and Affiliations

Priyanka Iyer[1] · Yubo Gao[2] · Diana Jalal[3] · Saket Girotra[4] · Namrata Singh[5] · Mary Vaughan-Sarrazin[6]

1 Division of Rheumatology, University of California at Irvine, Irvine, CA, USA

2 Division of General Medicine, Department of Internal Medicine, Roy and Lucille Carver College of Medicine, University of Iowa, Iowa City, IA, USA

3 Division of Nephrology, Department of Internal Medicine, Roy and Lucille Carver College of Medicine, University of Iowa, and Iowa City VA Health Care System, Iowa City, IA, USA

4 Division of Cardiology, Department of Internal Medicine, University of Iowa Roy and Lucille Carver College of Medicine, University of Iowa, and Iowa City VA Health Care System Center for Access and Delivery Research and Evaluation (CADRE), Iowa City, IA, USA

5 Division of Rheumatology, Department of Medicine, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195, USA

6 Division of General Medicine, Department of Internal Medicine, Roy and Lucille Carver College of Medicine, University of Iowa, and Iowa City VA Health Care System Center for Access and Delivery Research and Evaluation (CADRE), Iowa City, IA, USA