ORIGINAL RESEARCH ARTICLE

Digoxin and Standard-of-Care Therapy for Heart Failure Patients with COVID-19: Analysis of Data from the US Military Health System (MHS) Data Repository

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Abstract

Background Cardiac glycosides such as digoxin, digitoxin and ouabain are still used around the world to treat patients with chronic heart failure with reduced ejection fraction (HFrEF) and/or atrial fibrillation (AF). However, in the US, only digoxin is licensed for treating these illnesses, and the use of digoxin for this group of patients is increasingly being replaced in the US by a new standard of care with groups of more expensive drugs. However, ouabain and digitoxin, and less potently digoxin, have also recently been reported to inhibit SARS-CoV-2 virus penetration into human lung cells, thus blocking COVID-19 infection. COVID-19 is known to be a more aggressive disease in patients with cardiac comorbidities, including heart failure.

Objective We therefore considered the possibility that digoxin might provide at least a measure of relief from COVID-19 in digoxin-treated heart failure patients. To this end, we hypothesized that treatment with digoxin rather than standard of care might equivalently protect heart failure patients with regard to diagnosis of COVID-19, hospitalization and death.

Methods To test this hypothesis, we conducted a cross-sectional study by using the US Military Health System (MHS) Data Repository to identify all MHS TRICARE Prime and Plus beneficiaries aged 18–64 years with a heart failure (HF) diagnosis during the period April 2020 to August 2021. In the MHS, all patients receive equal, optimal care without regard to rank or ethnicity. Analyses included descriptive statistics on patient demographics and clinical characteristics, and logistic regressions to determine likelihood of digoxin use.

Results We identified 14,044 beneficiaries with heart failure in the MHS during the study period. Of these, 496 were treated with digoxin. However, we found that both digoxin-treated and standard-of-care groups were equivalently protected from COVID-19. We also noted that younger active duty service members and their dependents with HF were less likely to receive digoxin compared with older, retired beneficiaries with more comorbidities.

Conclusion The hypothesis of equivalent protection by digoxin treatment of HF patients in terms of susceptibility to COVID-19 infection appears to be supported by the data.

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Key Points

Heart failure patients with a moderate or severe Charlson Comorbidity Index (CCI) score were more likely than those with a mild score to receive digoxin.

The hypothesis of equivalent protection by digoxin treatment or standard of care of heart failure patients in terms of susceptibility to COVID-19 infection appears to be supported by the data.

In the Military Health System (MHS, with *ca.* 9.6 million members), it cannot be excluded that digoxin and standard of care protect heart failure patients equivalently from COVID-19.

1 Introduction

Cardiac glycosides such as digoxin, digitoxin, and ouabain are still used around the world to treat patients with chronic heart failure with reduced ejection fraction (HFrEF) and/or atrial fibrillation (AF) [1–6]. However, in the United States (US), only digoxin is licensed, and it has been increasingly replaced by a standard-of-care group of drugs which include renin-angiotensin aldosterone inhibitors (ARNI), β-blockers, mineralocorticoid receptor antagonists (MRA), and the SGLT2 inhibitor. However, a recent analysis using the Medical Expenditure Panel Survey (MEPS) showed that an increasing proportion of digoxin users in the US population at large are adults living at or below the federal poverty level [7]. Consistently, the yearly median out-of-pocket cost for standard of care is US$2217.00, whereas that for digoxin is only US$60.00. Other digoxin users in this category are those who self-identify as either Asian or Hispanic [7], and those with comorbidities which are inconsistent with standard of care [8, 9]. By contrast, the MEPS analysis also showed that digoxin use had declined among females and self-identified white adults [7].

Historically, because of the comorbidity problem, digoxin has been given, by design, both here in the US and elsewhere in the world, to the sickest patients who, by definition, have a higher mortality risk [6]. This strategy has caused previous clinical trials of digoxin to be subject to *prescription bias,* because digoxin was, by design, associated with lower overall survival [1, 6, 10]. However, current reexaminations of these older clinical trial data have led to the suggestion that use of digoxin may lead to overall survival outcomes "equal to or slightly better" than standard of care [3, 6, 11]. Consequently, digoxin may be experiencing a recurrence

of interest as reexamination of old clinical trial data has revealed that negative conclusions for both digoxin and digitoxin needed to be reconsidered [11–15].

However, because the COVID-19 pandemic has impacted profoundly on those with concomitant cardiovascular comorbidities [16], we considered whether digoxin-treated patients might be more susceptible to COVID-19 than those treated with standard of care. The reason for this consideration was that increased comorbidities, as defined by the Charlson Comorbidity Index (CCI), have been widely seen to be associated with worse outcomes for COVID-19 [17–20]. By contrast, it has been reported that digitoxin and ouabain, and with lesser potency digoxin, interfere with penetration of the SARS-CoV-2 virus into human lung cells [21] and green monkey kidney cells [22]. We therefore hypothesized that treatment with digoxin rather than standard of care might equivalently protect heart failure patients with regard to diagnosis of COVID-19, hospitalization and death.

2 Methods

To test this hypothesis, we conducted a cross-sectional study using the US Military Health System (MHS) Data Repository (MDR) to identify all MHS TRICARE Prime and Plus beneficiaries ages 18–64 years with a heart failure (HF) diagnosis during the COVID-19 pandemic (April 1 2020 to August 31 2021). The MDR contains administrative and clinically comprehensive data for 9.6 million beneficiaries, including active duty personnel, retirees, and their family members. In the MHS, all patients receive care through universal health coverage irrespective of rank, gender, or ethnicity. Beneficiaries aged 65 years and older were excluded from analyses due to TRICARE becoming secondary payer to Medicare. Beneficiaries associated with—either as personnel or dependents—the National Guard or Reserves were also excluded due to their inconsistent access to care.

We subsequently identified all persons in our study population diagnosed with COVID-19 or COVID-19-related conditions, and who received digoxin, β-blockers, ACE inhibitors, and angiotensin receptor blockers during the study period, as well as those who were hospitalized or died during the study period. The CCI score was retrospectively calculated by the authors for each patient at the time of their HF diagnosis using International Classification of Diseases, 10th revision (ICD-10), diagnostic codes and used to account for comorbidities and increased risk of disease. The full list of diagnostic codes used to identify heart failure and COVID-19 or related conditions can be found in the electronic supplementary material.

Study analyses included descriptive statistics on patient demographic and clinical characteristics; chi-square tests for differences in demographics and clinical characteristics

Table 1 Demographics and clinical characteristics of beneficiaries with heart failure during the period April 2020 to August 2021

	Total HF population (N = 14,044)	HF population with COVID-19 (n = 1490)	HF population without COVID-19 (n = 12,554)	Chi-square test p value
Gender				0.8376
Male	8781 (62.52)	928 (62.28)	7853 (62.55)	
Female	5263 (37.48)	562 (37.72)	4701 (37.45)	
Age group (y)				< 0.0001
18–24	629 (4.48)	102 (6.85)	527 (4.20)	
25–34	898 (6.39)	130 (8.72)	768 (6.12)	
35–44	1384 (9.85)	185 (12.42)	1199 (9.55)	
45–54	2871 (20.44)	324 (21.74)	2547 (20.29)	
55–64	8262 (58.83)	749 (50.27)	7513 (59.85)	
Race				0.0014, 0.0025[a]
White	6083 (43.31)	630 (42.28)	5453 (43.44)	
Black	3028 (21.56)	278 (18.66)	2750 (21.91)	
Asian/Pacific Islander	409 (2.91)	43 (2.89)	366 (2.92)	
American Indian/Alaska Native	77 (0.55)	11 (0.74)	66 (0.53)	
Other	760 (5.41)	106 (7.11)	654 (5.21)	
Missing	3687 (26.25)	422 (28.32)	3265 (26.01)	
Beneficiary status				< 0.0001, < 0.0001[a]
Active duty	1506 (10.72)	230 (15.44)	1276 (10.16)	
Dependent of other	4431 (31.55)	475 (31.88)	3956 (31.51)	
Dependent of active duty	986 (7.02)	110 (7.38)	876 (6.98)	
Retiree	7092 (50.50)	672 (45.10)	6420 (51.14)	
Missing	29 (0.21)	**	**	
Service/sponsor's service				0.6638
Army	5479 (39.01)	576 (38.66)	4903 (39.06)	
Air Force	4069 (28.97)	455 (30.54)	3614 (28.79)	
Navy	3308 (23.55)	336 (10.16)	2972 (23.67)	
Marine corps	862 (6.14)	91 (6.11)	771 (6.14)	
Other	326 (2.32)	32 (2.15)	294 (2.34)	
Rank/sponsor's rank				0.0004
Junior enlisted	750 (5.34)	107 (7.18)	643 (5.12)	
Senior enlisted	10256 (73.03)	1112 (74.63)	9144 (72.84)	
Junior officer	288 (2.05)	53 (3.56)	564 (4.49)	
Senior officer	1414 (10.07)	124 (8.32)	1290 (10.28)	
Other	1007 (7.17)	94 (6.31)	913 (7.27)	
Charlson Comorbidity Index				< 0.0001
No score	839 (5.97)	158 (10.60)	681 (5.42)	
Mild (1–2)	9775 (69.60)	949 (63.69)	8826 (70.30)	
Moderate (3–4)	2473 (17.61)	271 (18.19)	2202 (17.54)	
Severe (≥5)	957 (6.81)	112 (7.52)	845 (6.73)	
Receipt of select prescriptions				
Digoxin	496 (3.53)	51 (3.42)	445 (3.54)	0.8096
β-Blockers	9367 (66.70)	895 (60.07)	8472 (67.48)	< 0.0001
ACE inhibitors	4336 (30.87)	445 (29.87)	3891 (30.99)	0.3727
Angiotensin receptor blockers	3351 (23.86)	329 (22.08)	3022 (24.07)	0.0882
Admission for HF, COVID-19 or related condition	3805 (27.09)	668 (44.83)	3137 (24.99)	< 0.0001
COVID-19–related conditions				
Contact with and (suspected) exposure to COVID-19	3875 (27.59)	566 (37.99)	3309 (26.36)	< 0.0001

Table 1 (continued)

	Total HF population (N = 14,044)	HF population with COVID-19 (n = 1490)	HF population without COVID-19 (n = 12,554)	Chi-square test p value
Personal history of COVID-19	643 (4.58)	455 (30.54)	188 (1.50)	< 0.0001
Multisystem inflammatory syndrome	**	**	**	< 0.0001
Other specified systemic involvement of connective tissue	**	**	**	0.3986
Pneumonia due to COVID-19	366 (2.61)	**	**	< 0.0001
COVID-19 screening encounter	499 (3.55)	85 (5.70)	414 (3.30)	< 0.0001
Died during study period	273 (1.94)	49 (3.29)	224 (1.78)	< 0.0001

Data presented as n (col %)

HF heart failure

** Censored to protect patient anonymity due to small cell counts

[a]*p* value with missing values removed

between those with and without COVID-19; and unadjusted and adjusted logistic regressions, with multiple imputations for missing race, which were used to assess any demographic and clinical associations of COVID-19 diagnosis in HF patients. Twenty iterations and all patient demographics, CCI score categories, and receipt of digoxin status were used in the imputation of race. Parameter estimates and Akaike information criterion (AIC) fit statistics from full and complete case analysis models were compared with imputed results to assess the quality and fit of regression analysis. All patient demographics, CCI scores, and receipt of digoxin were used as adjustment factors in the adjusted logistic regression models. Additional subset analyses stratified by patient demographics and clinical characteristics were performed to determine impact of digoxin on patients with heart failure. All analyses were performed using SAS 9.4. This research was reviewed and determined exempt from human subjects oversight by the Uniformed Services University of the Health Sciences Institutional Review Board.

3 Results

We identified 14,044 beneficiaries with HFrEF during the study period. Of these, 10.6% were diagnosed with COVID-19; 3.5% were treated with digoxin; 27.1% were hospitalized; and 1.9% died during the study period. Among the subset diagnosed with COVID-19, 3.4% were treated with digoxin; 44.8% were hospitalized; and 3.3% died (Table 1). In addition, COVID-19 patients had systematically higher values of comorbidity above mild scores compared with those without COVID-19. Chi-square tests found differences across demographic and clinical characteristics, excluding gender, service, receipt of digoxin, ACE inhibitors and receptors, and other systemic and connective-tissue–related

conditions (Table 1). However, these differences in COVID-19 diagnosis were statistically insignificant (Table 2).

Nonetheless, multivariate logistic regressions with imputed race revealed statistically significant associations with age group, officer ranks, and mild CCI score category. For example, all age groups under the referent of 55–64 years were more likely to have COVID-19, with ages 18–24 years having the highest odds (OR 1.63; 95% CI 1.20–2.20). Those associated with Junior (OR 0.69, 95% CI 0.51–0.92) and Senior Officer ranks (OR 0.76, 95% CI 0.63–0.93) were less likely to have COVID-19 compared with those associated with a Senior Enlisted rank. However, patients with a mild CCI score (OR 0.57; 95% CI 0.47–0.71) were also less likely to receive digoxin when compared with patients with no score.

Descriptive and inferential statistics of data from patients prescribed digoxin can be found in Table 3. Use of Chi-square tests revealed statistically significant differences across age groups, beneficiary status, rank, and CCI score. In addition, multivariate logistic regression results found statistically significant associations among beneficiary status and CCI score only. Dependents of active duty personnel with HF were less likely to receive digoxin (OR 0.50, 95% CI 0.26–0.95) compared with retirees, and those with a moderate (OR 1.70, 95% CI 1.38–2.09) or severe CCI score (OR 1.60, 95% CI 1.18–2.18) were more likely than those with a mild score to receive digoxin.

4 Discussion

As hypothesized, these data indicate that digoxin, given to the HF patients with the most comorbidities, and standard of care given to those with the least comorbidities, equivalently protected against COVID-19. The hypothesis of equivalent protection by digoxin treatment of HF patients in terms of

Table 2 Odds of COVID-19 diagnosis among MHS beneficiaries with heart failure, April 2020 to August 2021

	Unadjusted OR (95% CI; p value)	Adjusted OR with imputed race (95% CI; p value)
Gender		
Female	1.01 (0.91–1.13; 0.8374)	0.97 (0.81–1.17; 0.7083)
Male (ref)	1	1
Age group (y)		
18–24	1.94 (1.55–2.43; < 0.0001)*	1.63 (1.20–2.20; 0.0021)*
25–34	1.70 (1.39–2.08; < 0.0001)*	1.59 (1.22–2.07; 0.0006)*
35–44	1.55 (1.30–1.84; < 0.0001)*	1.54 (1.25–1.89; < 0.0001)*
45–54	1.28 (1.11–1.47; 0.0005)*	1.31 (1.14–1.51; 0.0001)*
55–64 (ref)	1	1
Race		
White (ref)	1	1
Black	0.88 (0.75–1.02; 0.0778)	0.92 (0.73–1.15; 0.4247)
Asian/Pacific Islander	1.02 (0.73–1.41; 0.9198)	1.00 (0.73–1.36; 0.9229)
American Indian/Alaskan Native	1.44 (0.76–2.75; 0.2645)	1.26 (0.64–2.47; 0.3636)
Other	0.74 (0.47–1.17; 0.1935)	1.24 (0.98–1.55; 0.0741)
Beneficiary status		
Active duty	1.72 (1.47–2.02; < 0.0001)*	1.16 (0.92–1.46; 0.2110)
Dependent of active duty	1.20 (0.97–1.49; 0.0949)	0.98 (0.72–1.34; 0.4658)
Dependent of other	1.15 (1.01–1.30; 0.0300)*	1.15 (0.95–1.40; 0.7798)
Retiree (ref)	1	1
Rank/sponsor's rank		
Junior enlisted	1.37 (1.11–1.70; 0.0041)*	0.91 (0.71–1.18; 0.4849)
Senior enlisted (ref)	1	1
Junior officer	0.77 (0.58–1.03; 0.0797)	0.69 (0.51–0.92; 0.0109)*
Senior officer	0.79 (0.65–0.96; 0.0178)*	0.76 (0.63–0.93; 0.0066)*
Other	0.85 (0.68–1.06; 0.1402)	0.73 (0.57–0.93; 0.0111)*
Charlson Comorbidity Index category		
None	1	1
Mild	0.46 (0.39–0.56; < 0.0001)*	0.57 (0.47–0.71; < 0.0001)*
Moderate (ref)	0.53 (0.43–0.66; < 0.0001)*	–
Severe	0.57 (0.44–0.74; < 0.0001)*	0.77 (0.57–1.02; 0.0765)
Receipt of digoxin	–	–
Yes	0.97 (0.72–1.30; 0.8120)	1.01 (0.75–1.36; 0.9405)
No (ref)	–	–

Service was used as an adjustment factor and imputation predictions due to race not being equally represented across all service branches

CI confidence interval, MHS Military Health System, OR odds ratio

*Statistically significant with p < 0.05

susceptibility to COVID-19 infection thus appears to be supported by the data. Whether the same can be said for digitoxin, which is a more potent inhibitor of viral penetration [21], may soon be known when analysis is completed for the DIGIT-HF trial [1]. We are also aware that ouabain, the most potent inhibitor of viral penetration, may eventually have a role to play in viral defense. However, to the best of our knowledge, no trial is ongoing.

An additional inference from this analysis, at least as it might inform regarding current digoxin treatment in the US population at large, is that the socioeconomic relegation of digoxin to the poor, to certain ethic groups, and to those with relevant comorbidities [7] does not necessarily carry with it a poor outcome for either HF treatment or resistance to COVID-19. However, an important caveat is that optimal care, as provided by the MHS to all patients, could be contributing to the equivalent outcome.

Indeed, in contrast to the US population at large, the MHS population of the youngest patients, as marked by their representation as service members and their dependents, and

Table 3 Demographic and clinical comparisons of beneficiaries with heart failure and digoxin treatment status

	HF received digoxin (n = 496)	HF did not receive digoxin (n = 13,548)	Chi-square test p value	Adjusted odds ratios (95% CI), p value
Gender			0.5789	
Male	316 (63.71)	8465 (62.48)		1
Female	180 (36.29)	5083 (37.52)		0.98 (0.71–1.35), 0.8961
Age group (y)			< 0.0001	
18–24	11 (2.22)	618 (4.56)		1.19 (0.61–2.34), 0.5895
25–34	16 (3.23)	882 (6.51)		1.09 (0.60–1.98), 0.7805
35–44	30 (6.05)	1354 (9.99)		0.90 (0.60–1.37), 0.6237
45–54	97 (19.56)	2774 (20.48)		0.95 (0.75–1.20), 0.6220
55–64	342 (68.95)	7920 (58.46)		1
Race			0.8124, 0.6928[a]	
White	225 (45.36)	5858 (43.24)		1
Black	102 (20.56)	2926 (21.60)		0.84 (0.67–1.06), 0.0917
Asian/Pacific Islander	13 (2.62)	396 (2.92)		0.89 (0.53–1.51), 0.6361
American Indian/Alaska Native	**	**		**
Other	21 (4.23)	739 (5.45)		0.85 (0.54–1.32), 0.5973
Missing	132 (26.61)	3555 (26.24)		–
Beneficiary status			< 0.0001, < 0.0001[a]	
Active duty	17 (3.43)	1489 (10.99)		0.43 (0.24–0.77), 0.0038
Dependent of other	173 (34.88)	4258 (31.43)		0.97 (0.70–1.35), 0.8477
Dependent of active duty	17 (3.43)	969 (7.15)		0.50 (0.26–0.95), 0.0330
Retiree	289 (58.27)	6803 (50.21)		1
Missing	**	**		–
Service/sponsor's service			0.2729	
Army	188 (37.90)	5291 (39.05)		–
Air Force	160 (32.26)	3909 (28.85)		–
Navy	116 (23.39)	3192 (23.56)		–
Marine Corps	21 (4.23)	841 (6.21)		–
Other	11 (2.22)	315 (2.33)		–
Rank/sponsor's rank			0.0018	
Junior Enlisted	14 (2.82)	736 (5.43)		0.80 (0.45–1.42), 0.4361
Senior Enlisted	399 (80.44)	9857 (72.76)		1
Junior Officer	12 (2.42)	605 (4.47)		0.61 (0.34–1.10), 0.1059
Senior Officer	42 (8.47)	1372 (10.13)		0.85 (0.61–1.18), 0.3368
Other	29 (5.85)	978 (7.22)		0.97 (0.64–1.47), 0.8522
Charlson Comorbidity Index			< 0.0001	
No score	**	**		**
Mild (1–2)	306 (61.69)	9469 (69.89)		1
Moderate (3–4)	138 (27.82)	2335 (17.24)		1.70 (1.38–2.09), < 0.0001
Severe (≥ 5)	51 (10.28)	906 (6.69)		1.60 (1.18–2.18), 0.0028
COVID-19	51 (10.28)	1439 (10.62)	0.8096	1.02 (0.76–1.37), 0.9014
Receipt of select prescriptions				
β-Blockers	441 (88.91)	8926 (65.88)	< 0.0001	
ACE inhibitors	167 (33.67)	4169 (30.77)	0.1701	
Angiotensin receptor blockers	128 (25.81)	3223 (23.79)	0.3006	
COVID-19–related conditions				
Contact with and (suspected) exposure to COVID-19	170 (34.27)	3705 (27.35)	0.0007	
Personal history of COVID-19	21 (4.23)	622 (4.59)	0.7085	

Table 3 (continued)

	HF received digoxin (n = 496)	HF did not receive digoxin (n = 13,548)	Chi-square test p value	Adjusted odds ratios (95% CI), p value
Multisystem inflammatory syndrome	0	**	0.5450	
Other specified systemic involvement of connective tissue	**	**	0.6392	
Pneumonia due to COVID-19	11 (2.22)	355 (2.62)	0.5804	
Screening encounter for COVID-19	20 (4.03)	479 (3.54)	0.5573	
Admission for HF, COVID-19 or related condition	203 (40.93)	3602 (26.59)	< 0.0001	
Died during study period	13 (2.62)	260 (1.92)	0.2661	

Data presented as *n* (col %)

Service was used as an adjustment factor and imputation predictions due to race not being equally represented across all service branches. Due to the low proportions of no CCI score among those receiving digoxin, 'mild' score was selected as the referent group due to it having the highest proportions among both those who did and did not receive digoxin. Additional clinical characteristics from 'receipt of select prescriptions' and below were not included as predictors in the adjusted logistic regression model

HF heart failure, *CI* confidence interval

**Censored to protect patient anonymity due to small cell counts

[a]*p* value with missing values removed

independent of ethnicity, race or gender, are less frequently prescribed digoxin than the older patients/beneficiaries (see Table 2). The older beneficiaries have larger numbers of comorbidities than the younger active duty service members and their families, and are therefore more likely to be prescribed digoxin. Thus, the rationale for who is prescribed digitoxin to treat HF in the US population at large is the inverse of the MHS population. In addition, we noted that HF patients treated with digoxin were also more likely to be prescribed β-blocker drugs (see Table 3).

There are limitations to this study. It is a limitation that there is a smaller number of digoxin-treated patients compared with those receiving standard of care. However, this is also generally the case for the comparison study of the US population at large [7]. Furthermore, it is a limitation that the MHS patients were all in the age range of 18–64 years. However, the racial/ethnic/gender demographics of our two groups were comparable, thus providing further support for our findings, regardless of the limitations [7]. It is also a limitation that it cannot be excluded that digoxin-dependent blockade of SARS-CoV-2 penetration into target cells [21–23] may have contributed to successful resistance to COVID-19 infection by HF patients receiving digoxin. However, further tests of this possibility will have to be left for future studies. Furthermore, the use of administrative claims data can lead to underestimation of prevalence and comorbidities, and there is the potential for unseen confounders or biases; both points are additional limitations of the study. Lastly, this cross-sectional study can only provide observed associations; other criteria such as experimental study designs, temporality, and repeatability from further studies are needed to prove or disprove causation.

5 Conclusion

The hypothesis of equivalent protection by digoxin treatment of HF patients in terms of susceptibility to COVID-19 infection appears to be supported by the data. In the MHS (which has *ca*. 9.5 million members), it cannot be excluded that digoxin and standard of care protect HF patients equivalently from COVID-19.

Author's contributions All authors have read and approved the final submitted manuscript, and agree to be accountable for the work. HBP, ALB and TPK planned the study. ALB performed statistical analysis. HBP, TPK and ALB analyzed the data and wrote the paper. All authors meet the four ICMJE criteria for authorship.

Data Availability Statement The data that support the findings of this study are available from the United States Department of Defense, Defense Health Agency. Restrictions apply to the availability of these data, which were used under federal Data User Agreements for the current study, and so are not publically available.

Declarations

Code availability Not applicable.

Ethics Approval This research was reviewed and determined exempt from human subjects oversight by the Uniformed Services University of the Health Science's Institutional Review Board.

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