

Case 01 EC

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Table 1

Note: Digoxin = 1 and Placebo = 0. NAs have been removed in certain calculations when needed, resulting in some proportion fractions with different denominator from the total no. of patients in the group.

	0 (N = 3403)	1 (N = 3397)
Characteristics		
Age (yr) - mean (sd)	63.5 \pm 10.8	63.4 \pm 11.0
Ejection fraction - mean (sd)	28.4 \pm 8.9	28.6 \pm 8.8
Median duration of CHF - mo	16	17
% of patients		
Female sex	764 (22.5%)	755 (22.2%)
Nonwhite race	504 (14.8%)	487 (14.3%)
Age >70 yr	931 (27.4%)	906 (26.7%)
Cardiothoracic ratio >0.55	1,170/3,402 (34.4%)	1,176/3,396 (34.6%)
Previous digoxin use	1,519 (44.6%)	1,498 (44.1%)
Method of assessing ejection fraction		
Radionuclide ventriculography	2,184 (64.2%)	2,207 (65.0%)
Two-dimensional echocardiography	1,022 (30.0%)	1,003 (29.5%)
Contrast angiography	197 (5.8%)	187 (5.5%)
NYHA class		
I	442/3,401 (13.0%)	465/3,393 (13.7%)
II	1,854/3,401 (54.5%)	1,810/3,393 (53.3%)
III	1,039/3,401 (30.5%)	1,042/3,393 (30.7%)
IV	66/3,401 (1.9%)	76/3,393 (2.2%)
No. of signs or symptoms of CHF		
0	36 (1.1%)	39 (1.1%)
1	69 (2.0%)	80 (2.4%)
2	243 (7.1%)	240 (7.1%)
3	292 (8.6%)	315 (9.3%)
>=4	2,763 (81.2%)	2,723 (80.2%)
Medical history		
Previous myocardial infarction	2,221 (65.3%)	2,198/3,396 (64.7%)
Current angina	899/3,402 (26.4%)	922/3,396 (27.1%)
Diabetes	972 (28.6%)	961 (28.3%)
Hypertension	1,557 (45.8%)	1,527/3,396 (45.0%)
Concomitant medications		
Diuretics	2,797/3,402 (82.2%)	2,759/3,396 (81.2%)
ACE inhibitors	3,225 (94.8%)	3,197 (94.1%)
Nitrates	1,466 (43.1%)	1,432 (42.2%)
Other vasodilators	50/3,399 (1.5%)	32/3,391 (0.9%)

	0 (N = 3403)	1 (N = 3397)
Daily dose of study medication prescribed		
0.125mg	592 (17.4%)	593/3,396 (17.5%)
0.250mg	2,384 (70.1%)	2,399/3,396 (70.6%)
0.375mg	383 (11.3%)	350/3,396 (10.3%)
0.500mg	32 (0.9%)	36/3,396 (1.1%)
Primary cause of CHF		
Ischemic	2,398/3,394 (70.7%)	2,405/3,388 (71.0%)
Nonischemic	996/3,394 (29.3%)	983/3,388 (29.0%)
Primary cause of CHF - Nonischemic		
Idiopathic	482/3,394 (14.2%)	525/3,388 (15.5%)
Hypertensive	311/3,394 (9.2%)	272/3,388 (8.0%)
Other	203/3,394 (6.0%)	186/3,388 (5.5%)

Commentary

Overall, I have been able to reproduce the exact same results as the NEJM paper. There were only a few discrepancies where the results are off by a few decimal place.

In Table 1, the standard deviation of ejection fraction in the digoxin group is off by 0.1 (8.8 instead of 8.9). The proportion of patients in the digoxin group that are nonwhite (14.3% vs. 14.4%), or show ≥ 4 signs of CHF (80.2% vs. 80.1%), or had nitrates as concomitant medication (42.2% vs. 42.1%), or had other nonischemic cause of CHF (5.5% vs. 5.4%) are all off by 0.1%. The proportion of patients in the placebo group who had 0.250mg daily dose of study medication prescribed (70.1% vs. 70.0%), or had idiopathic (nonischemic) cause of CHF (14.2% vs. 14.1%) are also off by 0.1%. Lastly, for the proportion of patients with ischemic cause of CHF, the placebo group is off by 0.3% (70.7% vs. 70.4%) and the digoxin group is off by 0.2% (71% vs. 70.8%).

In Table 4, the no. of randomized patients in digoxin group with CT ratio ≤ 0.55 is off by 1 count (2221 vs. 2220) and the risk ratio for NYHA class (III or IV) is off by 0.01 (0.69 vs. 0.70).

These discrepancies could potentially be due to difference in my treatment of missing data and that of the paper.

Table 4

```
# no. of patients with >=1 event
subdig %>%
  group_by(ejection_fraction, treatment) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

Ejection fraction

ejection_fraction	Digoxin	Placebo
<0.25	428	556
0.25-0.45	613	735

```
# no. randomized
dig %>%
  group_by(ejection_fraction, treatment) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

ejection_fraction	Digoxin	Placebo
<0.25	1127	1130
0.25-0.45	2270	2273

```
# 0.25-0.45
prop_dig1 <- 613 / 2270
prop_placebo1 <- 735 / 2273
abs_diff_ci(prop_dig1, prop_placebo1, 2270, 2273)
```

```
## [1] "Absolute Difference and 95% CI in %: -5.3 (-8.0 to -2.7)"
```

```
# <0.25
prop_dig2 <- 428 / 1127
prop_placebo2 <- 556 / 1130
abs_diff_ci(prop_dig2, prop_placebo2, 1127, 1130)
```

```
## [1] "Absolute Difference and 95% CI in %: -11.2 (-15.3 to -7.2)"
```

```
# risk ratio
## 0.25-0.45
temp1 <- dig %>%
  filter(ejection_fraction == "0.25-0.45")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp1) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.80	0.72, 0.89	<0.001

```
## <0.25
temp2 <- dig %>%
  filter(ejection_fraction == "<0.25")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp2) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			

Characteristic	HR	95% CI	p-value
1	0.68	0.60, 0.77	<0.001

```
# no. of patients with >=1 event
subdig %>%
  group_by(treatment, prior_digoxin_use) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

Previous use of digoxin

prior_digoxin_use	Digoxin	Placebo
No	491	603
Yes	550	688

```
# no. randomized
dig %>%
  group_by(treatment, prior_digoxin_use) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

prior_digoxin_use	Digoxin	Placebo
No	1899	1884
Yes	1498	1519

```
# Yes previous use of digoxin
prop_dig1 <- 550 / 1498
prop_placebo1 <- 688 / 1519
abs_diff_ci(prop_dig1, prop_placebo1, 1498, 1519)
```

```
## [1] "Absolute Difference and 95% CI in %: -8.6 (-12.1 to -5.1)"
```

```
# No previous use of digoxin
prop_dig2 <- 491 / 1899
prop_placebo2 <- 603 / 1884
abs_diff_ci(prop_dig2, prop_placebo2, 1899, 1884)
```

```
## [1] "Absolute Difference and 95% CI in %: -6.2 (-9.0 to -3.3)"
```

```
# risk ratio
## Yes
temp1 <- dig %>%
  filter(DIGUSE == 1)
```

```
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp1) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.74	0.66, 0.83	<0.001

```
## No
temp2 <- dig %>%
  filter(DIGUSE == 0)
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp2) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.77	0.68, 0.86	<0.001

```
# no. of patients with >=1 event
subdig %>%
  filter(!is.na(cause)) %>%
  group_by(treatment, cause) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

Cause of heart failure

cause	Digoxin	Placebo
ischemic	731	873
nonischemic	306	413

```
# no. randomized
dig %>%
  filter(!is.na(cause)) %>%
  group_by(treatment, cause) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

cause	Digoxin	Placebo
ischemic	2405	2398
nonischemic	983	996

```
# ischemic cause of heart failure
prop_dig1 <- 731 / 2405
prop_placebo1 <- 873 / 2398
abs_diff_ci(prop_dig1, prop_placebo1, 2405, 2398)
```

```
## [1] "Absolute Difference and 95% CI in %: -6.0 (-8.7 to -3.3)"
```

```
# nonischemic cause of heart failure
prop_dig2 <- 306 / 983
prop_placebo2 <- 413 / 996
abs_diff_ci(prop_dig2, prop_placebo2, 983, 996)
```

```
## [1] "Absolute Difference and 95% CI in %: -10.3 (-14.5 to -6.1)"
```

```
# risk ratio
## ischemic
temp1 <- dig %>%
  filter(cause == "ischemic")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp1) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.79	0.72, 0.88	<0.001

```
## nonischemic
temp2 <- dig %>%
  filter(cause == "nonischemic")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp2) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.67	0.58, 0.77	<0.001

```
# no. of patients with >=1 event
subdig %>%
  group_by(treatment, ct_ratio) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

Cardiothoracic ratio

ct_ratio	Digoxin	Placebo
<=0.55	600	724
>0.55	441	567

```
# no. randomized
dig %>%
  group_by(treatment, ct_ratio) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

ct_ratio	Digoxin	Placebo
<=0.55	2221	2233
>0.55	1176	1170

```
# cardiothoracic ratio <=0.55
prop_dig1 <- 600 / 2221
prop_placebo1 <- 724 / 2233
abs_diff_ci(prop_dig1, prop_placebo1, 2221, 2233)
```

```
## [1] "Absolute Difference and 95% CI in %: -5.4 (-8.1 to -2.7)"
```

```
# cardiothoracic ratio >0.55
prop_dig2 <- 441 / 1176
prop_placebo2 <- 567 / 1170
abs_diff_ci(prop_dig2, prop_placebo2, 1176, 1170)
```

```
## [1] "Absolute Difference and 95% CI in %: -11.0 (-14.9 to -7.0)"
```

```
# risk ratio
## <=0.55
temp1 <- dig %>%
  filter(ct_ratio == "<=0.55")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp1) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.79	0.71, 0.88	<0.001

```
## >0.55
temp2 <- dig %>%
  filter(ct_ratio == ">0.55")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp2) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.69	0.61, 0.78	<0.001

```
# no. of patients with >=1 event
subdig %>%
  filter(!is.na(NYHA)) %>%
  group_by(treatment, NYHA) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

NYHA class

NYHA	Digoxin	Placebo
I or II	601	739
III or IV	438	552

```
# no. randomized
dig %>%
  filter(!is.na(NYHA)) %>%
  group_by(treatment, NYHA) %>%
  summarise(n = n()) %>%
  spread(treatment, n) %>%
  kable()
```

NYHA	Digoxin	Placebo
I or II	2275	2296
III or IV	1118	1105

```
# NYHA class (I or II)
prop_dig1 <- 601 / 2275
prop_placebo1 <- 739 / 2296
abs_diff_ci(prop_dig1, prop_placebo1, 2275, 2296)
```

```
## [1] "Absolute Difference and 95% CI in %: -5.8 (-8.4 to -3.1)"
```

```
# NYHA class (III or IV)
prop_dig2 <- 438 / 1118
prop_placebo2 <- 552 / 1105
abs_diff_ci(prop_dig2, prop_placebo2, 1118, 1105)
```

```
## [1] "Absolute Difference and 95% CI in %: -10.8 (-14.9 to -6.7)"
```



```
# risk ratio
## I or II
temp1 <- dig %>%
  filter(NYHA == "I or II")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp1) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.78	0.70, 0.87	<0.001

```
## III or IV
temp2 <- dig %>%
  filter(NYHA == "III or IV")
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = temp2) %>%
  gtsummary::tbl_regression(exp = TRUE)
```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.69	0.61, 0.79	<0.001

```
# no. of patients hospitalized/dead due to worsening heart failure
subdig %>%
  group_by(treatment) %>%
  summarise(n = n()) %>%
  kable()
```

Overall study population

treatment	n
Digoxin	1041
Placebo	1291

```
sub_ndig <- 1041
sub_nplacebo <- 1291

# overall study population
dig %>%
  group_by(treatment) %>%
  summarise(n = n()) %>%
  kable()
```

treatment	n
Digoxin	3397
Placebo	3403

```

ndig <- 3397
nplacebo <- 3403

prop_dig <- sub_ndig / ndig
prop_placebo <- sub_nplacebo / nplacebo
abs_diff_ci(prop_dig, prop_placebo, ndig, nplacebo)

## [1] "Absolute Difference and 95% CI in %: -7.3 (-9.5 to -5.0)"

# risk ratio
## overall study population
coxph(Surv(DWHFDAYS, DWHF) ~ TRTMT, data = dig) %>%
  gtsummary::tbl_regression(exp = TRUE)

```

Characteristic	HR	95% CI	p-value
TRTMT			
0			
1	0.75	0.69, 0.82	<0.001