**Supplementary material for the paper:**

Mixed comparison of stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Archives of Internal Medicine*

**EVIDENCE SYNTHESIS MODEL**

A random effects Poisson regression model (Spiegelhalter et al. 2004) was applied using the following model specification:

\[
\begin{align*}
    r_{jk} &\sim \text{Poisson}(\lambda_{jk}) \\
    \log(\lambda_{jk}) &= \begin{cases} 
    \log(py_{jk} / 1000) + \mu_{jb} & \text{if treatment } k = \text{treatment } b \\
    \log(py_{jk} / 1000) + \mu_{jb} + \delta_{jbk} & \text{if treatment } k \neq \text{treatment } b 
    \end{cases} \\
    \delta_{jbk} &\sim \text{Normal}(d_{bk}, V)
\end{align*}
\]

Where \(r_{jk}\) is the number of events and \(py_{jk}\) is the patient years of follow-up in trial \(j\) under treatment \(k\). \(\lambda_{jk}\) is the mean of Poisson distribution in trial \(j\) under treatment \(k\), \(\mu_{jb}\) is the log rate of an event (e.g. ischemic stroke, bleed, etc.) in trial \(j\) on baseline treatment \(b\), and \(\delta_{jbk}\) is the trial-specific log(rate ratio) of treatment \(k\) relative to treatment \(b\). \(d_{bk}\) is the pooled log(rate ratio) for treatment \(k\) relative to treatment \(b\) and \(V\) is the between-study variance parameter often referred to as the heterogeneity parameter as it estimates how much variation exists between the results of the different studies.

The model needs to take into account the correlation structure induced by the multi-arm trials; for example, multi-arm trials of A vs. B vs. C will induce a covariance between the trial-specific log rate ratios, \(\delta_{AB}\) and \(\delta_{AC}\). This correlation structure can be formulated by the decomposition of multivariate normal distribution as a series of conditional univariate distributions (Caldwell et al. 2005). If
\[
\begin{pmatrix}
\delta_{jbk1} \\
\vdots \\
\delta_{jbk_p}
\end{pmatrix}
\sim N
\left(
\begin{pmatrix}
d_{bk1} \\
\vdots \\
d_{bk_p}
\end{pmatrix}
\right)
, \begin{pmatrix}
\sigma^2 & \sigma^2/2 & \cdots & \sigma^2/2 \\
\sigma^2/2 & \sigma^2 & \cdots & \sigma^2/2 \\
\vdots & \vdots & \ddots & \vdots \\
\sigma^2/2 & \sigma^2/2 & \cdots & \sigma^2
\end{pmatrix}
\]

then the conditional univariate distributions are:

\[
\delta_{jb_{k1}} \mid \begin{pmatrix}
\delta_{bk1} \\
\vdots \\
\delta_{bk_{i-1}}
\end{pmatrix}
\sim N(d_{bk1} + \frac{1}{i} \sum_{j=1}^{i-1} (\delta_{jb_{kj}} - d_{bk_{j}}), \frac{(i+1)\sigma^2}{2i})
\]

The analyses were conducted in the freely available Bayesian software, WinBUGS\textsuperscript{20}.

Therefore, prior distributions needed to be specified for \(\mu_{jb}, d\) and \(V\). All prior distributions in this analysis were intended to be vague:

\[
\mu_{jb} \sim Normal(0, 0.0001) \quad d_{kb} \sim Normal(0, 0.0001) \quad \sqrt{V} \sim Uniform(0, 10)
\]

The goodness-of-fit of the model to the data was measured by calculating the residual deviance

\[
\bar{D}_{res} = -2 (\log lik_{model} - \log lik_{saturated})
\]

Where \(\log lik_{model}\) and \(\log lik_{saturated}\) are the deviances for the fitted model and the saturated model respectively. The deviance measures the fit of the model to the data points using the likelihood function. For Poisson data, the residual deviance is given by:

\[
\bar{D}_{res} = 2 \sum_j \sum_k r_{jk} \ln \left( \frac{r_{jk}}{\hat{r}_{jk}} \right) - (r_{jk} - \hat{r}_{jk}) = \sum_j \sum_k dev_{jk}
\]

Where \(r_{jk}\) is the observed number of events (i.e. ischemic stroke or bleed) and \(\hat{r}_{jk}\) is the expected number of events estimated from the current model for \(j = 1\) to \(J\) trials.
and $k$ represents the treatments compared in trial $j$. Under the null hypothesis that the model provides an adequate fit to the data, it is expected that $\bar{D}_{res}$ would have a mean equal to the number of unconstrained data points.

References:


WinBUGS code for mixed treatment comparisons

model
{
  for(i in 1:ns)
  {
    w[i,1] <- 0
    delta[i,t[i,1]]<-0
    mu[i] ~ dunif(-10,10)  # vague priors for
  
  trial baselines
  for (k in 1:na[i])
  {
    r[i,t[i,k]] ~ dpois(lambda[i,t[i,k]])  # Poisson distribution
    log(lambda[i,t[i,k]])<-log(py[i,t[i,k]]/1000)+mu[i]+delta[i,t[i,k]]  # evidence
  }
  for (k in 2:na[i])
  {
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])  # trial-specific log rate ratio
    md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]  # mean of LRR distribution
    taud[i,t[i,k]] <- tau * 2*(k-1)/k  # precision of LRR distribution
    w[i,k] <- delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]]  # adjustment, multi-arm RCTs
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)  # cumulative adjustment for multi-arm trials
  }
}

d[1]<-0
for (k in 2:nt)
{
  d[k] ~ dunif(-10,10)  # vague priors for basic parameters
}

sd~dunif(0,2)  # vague prior for random effects

standard deviation

tau<-1/pow(sd,2)

for (i in 1:ns)
{
  mu1[i] <- mu[i] * equals(t[i,1],1)
}

for (k in 1:nt)
{
  log(T[k])<- sum(mu1[1])/nb +d[k]
}

for (k in 1:nt)
{
  rk[k]<- rank(T[],k)
  best[k]<-equals(rk[k],1)  #Ranking treatments
  #Proportion each treatment the ‘best’
}

for (c in 1:(nt-1))
{
  for (k in (c+1):nt)
  {
    rr[c,k] <-exp(d[k]-d[c])
  }
}

#Pairwise rate ratio
#Data
list(nt= 9,ns=19, nb=8)


        ....
        ....
END