

Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Review and Meta-Analysis Comparing Patients With and Without Diabetes

Running Title: Aspirin for Primary Prevention in Diabetes

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Objective - The negative results of two randomized controlled trials (RCT) have challenged current guideline recommendations for using aspirin for primary prevention of cardiovascular events among patients with diabetes. We therefore sought to determine if the effect of aspirin for primary prevention of cardiovascular events and mortality differs between patients with and without diabetes.

Research Design and Methods - We conducted a systematic search of MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus since their inception until November 2008 for RCTs of aspirin for primary prevention of cardiovascular events. Blinded pairs of reviewers evaluated studies and extracted data. Random effects meta-analysis and Bayesian logistic regression were used to estimate the ratios of relative risks of outcomes of interest among patients with and without diabetes. A 95% confidence interval (CI) that crosses 1.00 indicates that the effect of aspirin does not differ between patients with and without diabetes.

Results - Nine RCTs with moderate to high methodological quality contributed data to the analyses. The ratios of relative risks comparing the benefit of aspirin among patients with diabetes compared to patients without diabetes for mortality, myocardial infarction and ischemic stroke were 1.12 (95% CI, 0.92, 1.35), 1.19 (95% CI, 0.82, 1.17) and 0.70 (95% CI, 0.25, 1.97), respectively.

Conclusions - While estimates of benefit among patients with diabetes remain imprecise, our analysis suggests that the relative benefit of aspirin is similar in patients with and without diabetes.

Cardiovascular events including myocardial infarction and ischemic stroke are the leading cause of morbidity and mortality in patients with diabetes, and the population burden of cardiovascular disease attributed to diabetes appears to be increasing (1). Several guidelines, including those of the American Diabetes Association (6), recommend aspirin for the primary prevention of cardiovascular events in patients with diabetes (4; 5). Given that trials of aspirin for primary prevention have enrolled too few patients with diabetes (6), guideline panels have applied indirect evidence from other high-risk groups to formulate this recommendation (12). In contrast, other guidelines such as the European Society of Cardiology and the European Association for the Study of Diabetes (4) and the most recent U.S. Preventive Services Task Force (13) provide no specific recommendations regarding the use of aspirin in patients with diabetes.

The best available estimate of the effect of aspirin comes from the most recent study from the Antithrombotic Trialists' Collaborative, an individual level meta-analysis of randomized controlled trials (RCTs) that reported a 12% reduction in the rate ratio of serious vascular events in patients with diabetes randomized to aspirin prophylaxis, although this finding was not statistically significant (rate ratio 0.88, 95% confidence interval 0.67-1.15) (4). However, this meta-analysis did not include data from the Early Treatment Diabetic Retinopathy Study (15) nor two recent primary prevention RCTs, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) (16) and the Prevention Of Progression of Arterial Disease and

Diabetes (POPADAD) (17) studies. Results from both JPAD and POPADAD, however, were imprecise and unable to exclude a reduction in the risk for their composite endpoints of up to 42% and 24%, respectively.

We, therefore, set out to conduct a systematic review of RCTs of aspirin for primary prevention in patients with diabetes to (a) estimate the efficacy of aspirin for the primary prevention of cardiovascular events among patients with diabetes, and (b) to estimate the extent to which the effect of aspirin differs in patients with and without diabetes.

RESEARCH DESIGN AND METHODS

The report of this protocol-driven systematic review adheres to the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of randomized clinical trials (18)

Eligibility criteria. Eligible studies were RCTs that enrolled patients with diabetes without a prior history of myocardial infarction or stroke, and assessed the efficacy of aspirin at any dosage.

Study identification and retrieval. An expert reference librarian designed and conducted the electronic search strategy. Our systematic search included MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus, since their inception until November 2008. We used database-specific controlled language and terms that describe the key concepts: aspirin, diabetes, cardiovascular events, prevention, and randomized trials. We also reviewed the reference sections of identified reviews, published guidelines, and published manuscripts known to the

authors. Study inclusion was not limited by publication status or language.

Pairs of reviewers, working independently and in duplicate, identified potentially eligible records for full text retrieval from the titles and abstracts. Records in which the reviewers disagreed were also retrieved in full text. Pairs of reviewers working independently and in duplicate reviewed the retrieved full text articles for eligibility. An independent reviewer resolved disagreements.

Outcomes. The outcomes of interest were ischemic stroke, myocardial infarction, and all-cause mortality.

Data abstraction. Two reviewers extracted the following data from each eligible article: description of study participants, study characteristics and outcome data.

Quality assessment. Independent reviewers working in duplicate determined the extent to which trials reported concealment of allocation, blinding of patients, providers and outcome assessors, and the extent of loss to follow-up.

Author contact. We contacted the corresponding and/or first author of each eligible article identified in the screening process by e-mail to confirm data extraction and quality assessment and to request missing information.

Prevention of cardiovascular events with aspirin. We used the kappa statistic to quantify chance-adjusted agreement between reviewers for article selection. Random effects meta-analyses estimated pooled treatment effects (relative risks [RR] and their 95% CI) of aspirin in preventing cardiovascular events and all-cause death in patients with diabetes and without diabetes. The I^2 statistic estimated the percentage of inconsistency across studies that was

due to heterogeneity rather than chance or random error (19).

Given that subjects included in the Antiphospholipid Antibody-Acetylsalicylic Acid (APLASA) study were receiving aspirin for antiphospholipid antibody syndrome and had a short duration of follow up, and a small number of subjects in the Early Treatment Diabetic Retinopathy Study (ETDRS) had suffered a prior stroke or myocardial infarction, we conducted sensitivity analysis to determine whether the exclusion of these studies affected the conclusions of this review.

Interaction between the effect of aspirin and diabetes status. We implemented three methods to determine whether a difference exists in aspirin effect in patients with and without diabetes. First, we estimated the ratio of relative risks and its 95% CI using the method of Altman (20). This estimate compares the pooled RRs across subgroups of patients with diabetes and without across trials. Pooled estimates that exclude a ratio of 1 provide evidence of an aspirin-diabetes interaction. Second, we estimated the ratio of relative risks comparing the aspirin effect in patients with and without diabetes *within* trials, and then pooled these ratios. Again, pooled estimates that exclude a ratio of RR of 1 indicate a statistically significant difference in the treatment effect of aspirin in patients with and without diabetes. We used Comprehensive Meta-Analysis version 2 software (Biostat Inc, Englewood, NJ) and StatsDirect 2.5.4 (StatsDirect Ltd, Cheshire, England) to conduct these analyses. Finally, we conducted a Bayesian random effects logistic regression with aspirin use and diabetes status as main effect factors and an interaction term of these two was also

applied to the included trials. A 95% credible interval of the regression coefficient of the interaction term that excludes 0 indicates that the effect of aspirin is different in patients with and without diabetes. This analysis was carried out using WinBUGS 1.4 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) with non-informative prior distributions and three parallel Markov Chain Monte Carlo chains with over-dispersed initials. The Brooks-Gelman-Rubin(21) convergence diagnostic was applied to examine the convergence of the Markov Chain Monte Carlo samplers. Statistical inferences were then drawn based on the resulting posterior distributions of parameters of interest. For RCTs with zero events in one study arm, we used a continuity correction factor of 0.5 and conducted sensitivity analysis using the treatment arm method to test whether the choice of statistical methods affected study conclusions (22).

RESULTS

Search results. Figure 1 describes the process of study selection that yielded 8 eligible RCTs for meta-analysis. The study by Zabel-Langhennig (23) did not report any events of interest and therefore was not included in the main analysis. Table 1 describes the included studies showing important differences in studies. Authors from 50% of eligible RCTs responded to our data requests (16; 24-26).

Methodological quality. Table 2 shows the methodological quality of the included RCTs. The kappa statistic for quality assessment identified through the screening process was 0.70 (range 0.64-0.87). Overall, trials had high methodological quality with more than

half of them concealing allocation and blinding patients and caregivers; most reporting minimal loss to follow up and only one was stopped earlier than planned because of finding significant benefit during an interim analysis.

Prevention of cardiovascular events with aspirin. Figures 2A, 2B, and 2C demonstrate the pooled RR and 95% CI for the effect of aspirin versus control on death, myocardial infarction and ischemic stroke, respectively, stratified by diabetes status. The estimates of RR and 95% CI among all patients regardless of diabetes status for the outcomes of mortality, myocardial infarction and ischemic stroke were 0.93 (CI, 0.85-1.03; $I^2=0\%$), 0.79 (CI, 0.66-0.95; $I^2=63\%$), and 0.73 (CI, 0.43-1.22; $I^2=39\%$), respectively. Estimates among patients with diabetes were 0.97 (CI, 0.87-1.08; $I^2=0\%$), 0.86 (CI, 0.67-1.11; $I^2=53\%$) and 0.62 (CI, 0.31-1.24; $I^2=67\%$), respectively. The corresponding estimates among patients without diabetes were 0.87 (CI, 0.75-1.02; $I^2=0\%$), 0.72 (CI, 0.55-0.95; $I^2=70\%$) and 0.89 (CI, 0.41-1.94; $I^2=0\%$), respectively.

Interaction between the effect of aspirin and diabetes status. Table 3 describes the results of between-study subgroup analysis, within-study subgroup analyses and Bayesian random-effects regression analyses. All three methods yielded nonsignificant ratios of relative risks of aspirin in patients with and without diabetes across all outcomes examined. The choice of continuity correction method for RCTs with zero-events in one arm did not substantially affect inferences.

Sensitivity analysis. Our conclusions were not significantly altered by the exclusion of the APLASA ($P_{\text{interaction}}$ 0.28, 0.36, and 0.63, for mortality, myocardial infarction, and ischemic stroke, respectively) or ETDRS trials

($P_{\text{interaction}}$ 0.18, 0.62, and 0.48, for mortality, myocardial infarction, and ischemic stroke, respectively).

CONCLUSIONS

Consistent with prior studies (14; 16; 17), we found no significant benefit of aspirin therapy for the primary prevention of cardiovascular events among patients with diabetes. Even for the outcome of myocardial infarction in which the overall risk reduction was statistically significant, our estimated risk reduction among patients with diabetes remained non-significant. However, our estimates were imprecise and unable to exclude a treatment benefit of 13%, 33%, and 69% for the outcomes of mortality, myocardial infarction and ischemic stroke, respectively. Using a between-studies approach, a within-studies approach, and a Bayesian analysis, we found evidence that the effect of aspirin among patients with diabetes was not significantly different from patients without diabetes. Thus, the data we present here provides imprecise evidence of benefit from using aspirin in patients with diabetes without a history of cardiovascular events; this treatment effect does not differ significantly from that observed in patients without diabetes.

Limitations and strengths. The main limitation of our study relates to our use of published aggregate data and lack of statistical power. The possibility of publication bias cannot be adequately assessed and corrected given the small number of RCTs (27). Our comprehensive literature search minimized the risk of publication and reporting biases, although our author response rate was relatively low and resulted in less complete data. It is possible that other aspirin RCTs have examined diabetes subgroups but have

not reported these results because of lack of a significant aspirin-diabetes interaction. If this were to be the case, their inclusion would likely strengthen our conclusions. The small number of included trials and the small number of events within these trials reduced the statistical power and therefore the precision of the estimates in our main analysis and in our tests for interaction between aspirin effect and diabetes status. Our analyses using multiple statistical methods to examine the diabetes-aspirin interaction and their consistent results contribute to strengthen our conclusions. While the use of composite endpoints would have increased our statistical power, we chose to pool individual endpoints because the composite endpoints in the included trials represent outcomes with large gradients in importance to patients and in potential magnitude of the effect of treatment across component end points (28). We did not examine the potential harm from aspirin therapy such as gastrointestinal bleeding since these events in the small population of patients with diabetes included in RCTs are likely rare, leading to imprecise estimates. Hence, evidence about harm is better obtained from larger studies that include patients without diabetes.

Implications. Our inferences should be considered in the context of proposed criteria to evaluate the validity of a subgroup effect (29). Good evidence of a valid subgroup effect results from testing few *a priori* hypotheses based on strong biological rationale. The extent to which this is true for the diabetes subgroup analyses reported in the literature is unclear to us. Our analyses, however, do not support other criteria for a valid subgroup effect. We found that differences in aspirin treatment effect

between patients with and without diabetes, both *between* and *within* RCTs, were inconsistent and of small magnitude. Thus, the current best evidence suggests that the efficacy of aspirin for the primary prevention of cardiovascular events in patients with diabetes is similar to that in patients without diabetes.

The decision to use aspirin for primary prevention in individual patients with diabetes remains a complex issue. Ultimately, the decision to use aspirin for an individual patient should consider the advantages and disadvantages of this preventive treatment given the patient's context and preferences. We suggest first estimating the 10-year risk of coronary heart disease (30; 31). Multiplying this estimate by 0.88 (12% relative risk reduction with the use of aspirin based on data from the Antithrombotic Trialists' Collaborative data (14)) would provide the revised 10-year risk estimate for a patient using aspirin. This should be presented alongside the risk of major gastrointestinal and extracranial bleeds with and without aspirin (14; 32). A patient decision aid could present these data to help patients and clinicians

consider the relative merits and downsides of aspirin use, as was done recently for use of statin therapy in patients with diabetes (33).

Summary. While there are insufficient data among patients with diabetes to conclusively show a benefit of aspirin therapy for the primary prevention of cardiovascular events, our data suggest, but do not confirm, that the relative benefit of aspirin is similar in patients with and without diabetes. Additional evidence from RCTs and individual-patient-data meta-analyses may help to further clarify this issue.

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Table 1. Description of included trials

Included trials	Patient population	Inclusion age (years)	Participants (% female)	Participants with DM (%)	Aspirin treatment	Control	Average study duration (years)	DM subgroup outcomes reported
APLASA (25)	Persistently antiphospholipid antibody-positive patients	≥18	98 (90)	6 (6)	81 mg daily	Placebo	2.3	Mortality, MI, stroke
HOT (26; 34)	Patients with hypertension	50-80	18,790 (47)	1,501(8)	75 mg daily	Placebo	3.8	Mortality, MI
ETDRS (15)	Patients with diabetes and diabetic retinopathy	18-70	3,711 (44)	3,711 (100)	650 mg daily	Placebo	5.0	Mortality, MI
JPAD (16)	Patients with diabetes mellitus type 2	30-85	2,539 (45)	2,539 (100)	81 or 100 mg daily	Open label	4.4	Mortality, MI, stroke
PHS (35)	Healthy male physicians	≥40	22,071 (0)	533 (2)	325 mg every other day	Placebo	5.0	MI
POPADAD (17)	Patients with diabetes and asymptomatic PAD and no symptomatic cardiovascular diseases	≥40	1,276 (56)	1,276 (100)	100 mg daily	Placebo	6.7	Mortality, MI
PPP (36)	Patients without history of CVD	≥50	1,031(52)	1,031 (100)	100 mg daily	Open label	3.6	MI, stroke
WHS (24)	Female healthcare professionals without CVD	≥45	39,876 (100)	1,037 (3)	100 mg every other day [†]	Placebo	10.1	MI, stroke

Abbreviations: APLASA, Antiphospholipid Antibody-Acetylsalicylic Acid; CVD, cardiovascular disease; DM, diabetes mellitus; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI, myocardial infarction; PAD, peripheral arterial disease; PHS, Physicians' Health Study; POPADAD, The Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; WHS, Women's Health Study

* Also randomized to vitamin E

† Also randomized to beta carotene

Table 2. Risk of bias in included trials

Study	Blinding-caregivers	Blinding-patients	Blinding-outcome assessors	Blinding-data collectors	Allocation concealment	Lost-to-follow up	Funding source	Trial stopped early
APLASA	Yes	Yes	Yes	Yes	Yes	5%	FP	No
ETDRS	Yes	Yes	Yes	Yes	Yes	>10%	NFP	No
HOT	Yes	Yes	Yes	No	Yes	3%	FP	No
JPAD	No	No	Yes	Yes	Yes	8%	NFP	No
PHS	Yes	Yes	Yes	NR/NC	NR/NC	<1%	FP	No
POPADAD	Yes	Yes	Yes	Yes	Yes	<1%	FP	No
PPP	No	No	NR	No	Yes	NR/NC	FP	Yes
WHS	Yes	Yes	Yes	No	NR/NC	NR/NC	FP	No

Abbreviations: APLASA, Antiphospholipid Antibody-Acetylsalicylic Acid; FP, Includes for-profit sources, HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; NFP, does not include for profit sources; NR/NC, profit status not reported or not clear; PHS, Physicians' Health Study; POPADAD, The Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; WHS, Women's Health Study

Table 3. Aspirin-diabetes subgroup interaction analyses

Outcome	RR [*] with Diabetes	RR [*] without Diabetes	P _{interaction}	Ratio of RR's Pooled across trials [†]	Ratio of RR's Pooled within trials [‡]	Ratio of RR's Bayesian analyses [§]
Mortality	0.97 (0.87-1.08)	0.87 (0.75-1.02)	0.28	1.12 (0.92-1.35)	1.00 (0.53-1.88)	1.16 (0.09, 13.79)
Myocardial infarction	0.86 (0.67-1.11)	0.72 (0.55-0.95)	0.36	1.19 (0.82-1.17)	1.02 (0.71-1.47)	1.06 (0.16, 6.71)
Ischemic stroke	0.62 (0.31-1.24)	0.89 (0.41-1.94)	0.50	0.70 (0.25-1.97)	0.93 (0.37-2.34)	0.47 (<0.01, 20.52)

Abbreviations: RR, relative risk

^{*} Random effects model is used in all meta-analyses. Numbers in parentheses represent 95% confidence intervals.

[†] Ratios of relative risks in this method are pooled across randomized controlled trials and subgroups of randomized controlled trials of patients with diabetes versus without diabetes; then a ratio of pooled estimates is estimated. Numbers in parentheses represent 95% confidence intervals, which indicate a significant interaction if it excludes 1.

[‡] Ratios of relative risks in this method are estimated within each randomized controlled trial, and then pooled. Confidence intervals that exclude 1 indicate a significant interaction. Numbers in parentheses represent 95% confidence intervals, which indicate a significant interaction if it excludes 1.

[§] Analysis conducted using Bayesian random effects logistic regression. Numbers in parentheses represent 95% credible intervals

Figure 1: Study process selection

Flow diagram of the process of study selection. Abbreviations: CV, cardiovascular

Figure 2: Forest plots for mortality, myocardial infarction and ischemic stroke

Forest plots of random effects meta-analysis for pooled relative risks of mortality (A), myocardial infarction (B) and ischemic stroke (C). Results are presented for patients with and without diabetes, and for all patients combined. Squares and horizontal lines represent the point estimates and associated 95% confidence interval (CI). The diamonds represent the pooled relative risk, with the center representing the point estimate and the width representing the associated 95% CI.

Figure 1

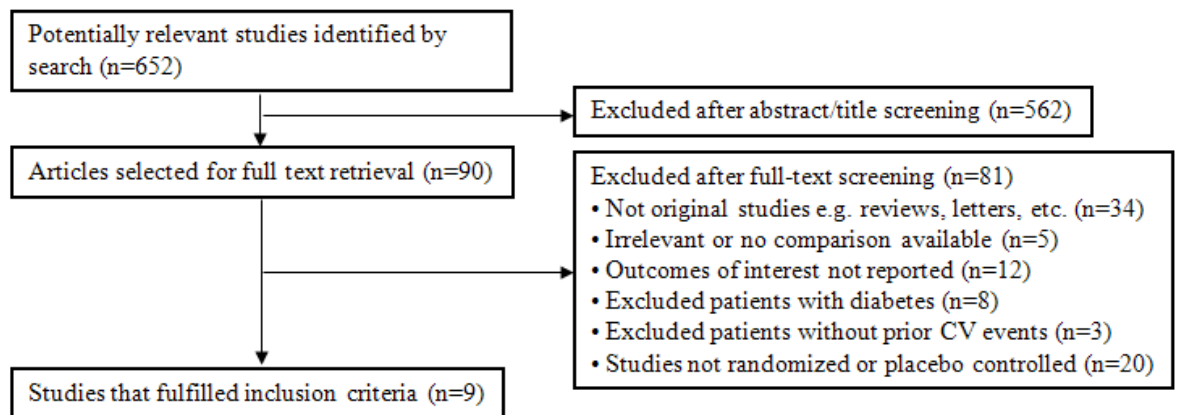


Figure 2A. Mortality

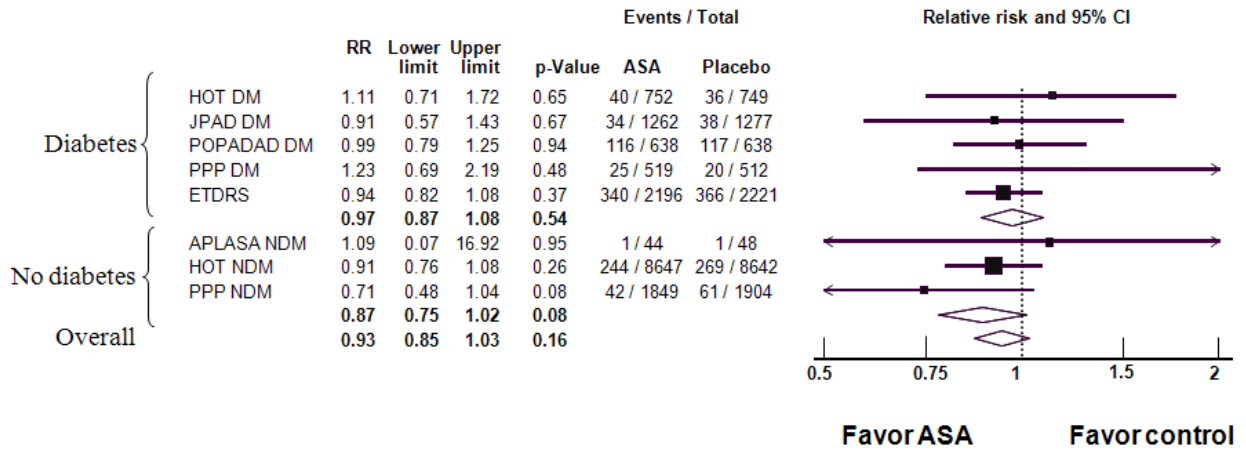


Figure 2B. Myocardial Infarction

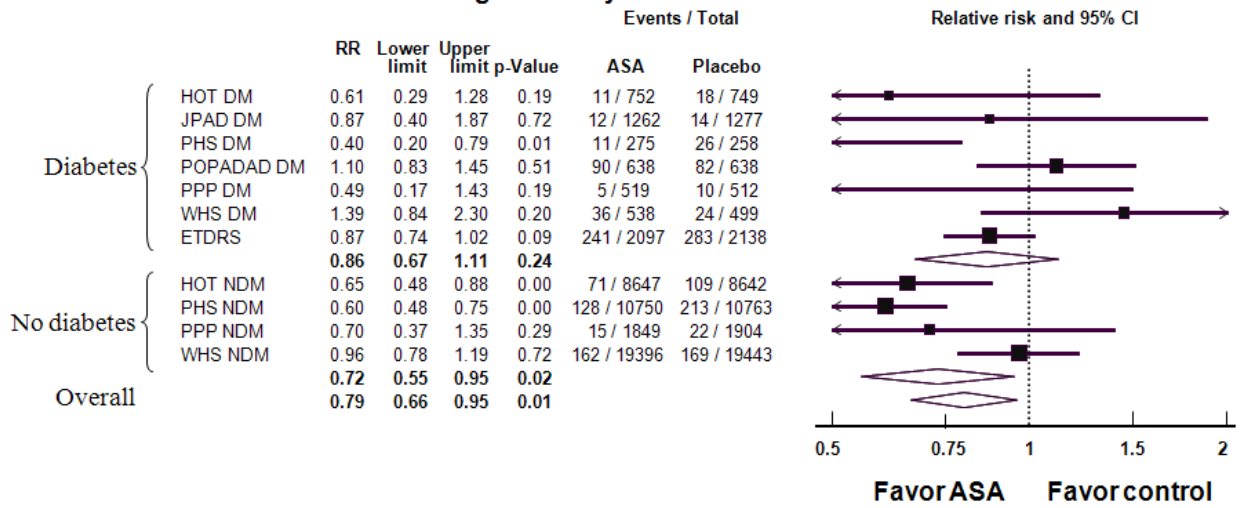


Figure 2C. Ischemic stroke

