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Culprit Only PCI in STEMI
Evidence is Not Yet Enough to Abandon

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DISCLOSURES

- CardiacAssist, Inc
  - Medical Director
  - Stock options
- Abbott Vascular, Inc
  - Consultant
  - Research support
- St Jude, Inc
  - Speaker Bureau

BACKGROUND

- Primary PCI is the default therapy for STEMI with class I A indication
- In patients with MVD there remains a continuing controversy re revascularization strategy in STEMI in the absence of CGS
- MV PCI in STEMI remains a Class III indication in the 2013 ACC/AHA guidelines based on a consensus conclusion of the writing committee

RATIONALE FOR MVD PCI in STEMI

- In patients presenting with STEMI 30-60% have significant MVD with increased morbidity and mortality compared to patients with SVD
- Normal compensatory mechanism of non-infarct zone is compensatory hyperkinesis, but in MVD, non-infract zone may become hypokinetic or dyskinetic
- Decreased epicardial flow and microvascular flow in non-infarct zones with decreased CFR is predictive of increased mortality
- Interventional Rx of STEMI has evolved remarkably over the past three plus decades with Primary PCI the recognized default Rx resulting in a precipitous decline in IH and long-term mortality. In the current DES era, can PCI in STEMI be extended to MV intervention?

Why Might MVI in STEMI BE UNSAFE?

- PCI is riskier in general in the setting of hemodynamic instability and LV dysfunction
- Prothrombotic and inflammatory milieu in the early phase of AMI may increase risk
- Lesion severity in nonculprit vessels may be overestimated at the time of PPCI because of diffuse vasoconstriction and systemic endothelial dysfunction
- MV PCI increases contrast load which may be less well tolerated in terms of renal and myocardial function
- Complications in the nonculprit vessel may be poorly tolerated with hypotension and resultant acute stent thrombosis in both vessels

STRATEGIES IN PRIMARY PCI

In non-shock patients

- Culprit vessel only
- Culprit vessel + non-culprit vessel(s) in single setting
- Culprit vessel + non-culprit vessel(s) as staged procedure

We assume that all patients receive the best GDMT

STUDIES OF CULPRIT ONLY VS MVPCI in STEMI

What are the Data?

- Prospective Registries and Retrospective Analyses
- Meta-Analyses
- Sophisticated statistical gymnastics required to account for all the confounding variables
- Majority of studies are retrospective and only a few were performed in the contemporary era of PCI technique with widespread use of DES and potent antithrombotic agents
- Randomized Controlled Trials

The PRAMI Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Preventive Angioplasty in Myocardial Infarction

David S. Wald, M.D., Joan K. Morris, Ph.D., Nicholas J. Wald, F.R.S., Alexander J. Chase, M.B., B.S., Ph.D., Richard J. Edwards, M.D., Liam O. Hughes, M.D., Colin Berry, M.B., Ch.B., Ph.D., and Keith G. Oldroyd, M.D., for the PRAMI Investigators*

The N Engl J of Med 2013;369:1115-1123

The PRAMI Trial

- 465 Patients with acute STEMI in 5 centers between 2008-2013
- RCT - Preventive PCI vs No Preventive PCI
- Subsequent PCI only for refractory angina with objective evidence of ischemia
- Primary EP - composite of cardiac death, non-fatal MI, or refractory angina
- Conclusion: In patients with MV CAD undergoing infarct artery PCI, preventive PCI in non-infarct coronary arteries significantly reduced the risk of adverse CV events, as compared with PCI limited to the infarct artery

Wald *et al The N Engl J of Med* 2013;369:1115-1123

The PRAMI Trial
"A Straw Man"

- After completion of PCI in the infarct artery, eligible pts were randomized to undergo **no further PC**I or to undergo **immediate PCI** in noninfarct arteries with more than 50% stenoses (preventive PCI)
- **Staged PCI** in pts without AP was **discouraged** The intention of the investigators was that further PCI for AP should be performed only in cases of refractory AP

The PRAMI Trial
"A Straw Man"

In other words

- It was acceptable to stent a 50% stenosis in a noninfarct vessel at the time of primary PCI
- But it was unacceptable to do a "staged PCI" in a 90% stenosis of a major epicardial vessel if the patient is asymptomatic
- And a subsequent revascularization in this vessel is counted as MACE
- We also know that there are many 50% and 70% stenoses that are not physiologically significant

The PRAMI Trial

Table 3. Prespecified Clinical Outcomes.*

Outcome	Preventive PCI (N=234)	No Preventive PCI (N=231)	Hazard Ratio (95% CI)	P Value
	no. of events			
Primary outcome				
Death from cardiac causes, nonfatal myocardial infarction, or refractory angina†	21	53	0.35 (0.21–0.58)	<0.001
Death from cardiac causes or nonfatal myocardial infarction†	11	27	0.36 (0.18–0.73)	0.004
Death from cardiac causes	4	10	0.34 (0.11–1.08)	0.07
Nonfatal myocardial infarction	7	20	0.32 (0.13–0.75)	0.009
Refractory angina	12	30	0.35 (0.18–0.69)	0.002
Secondary outcomes				
Death from noncardiac causes	8	6	1.10 (0.38–3.18)	0.86
Repeat revascularization	16	46	0.30 (0.17–0.56)	<0.001

Wald *et al The N Engl J of Med* 2013;369:1115-1123

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Questions

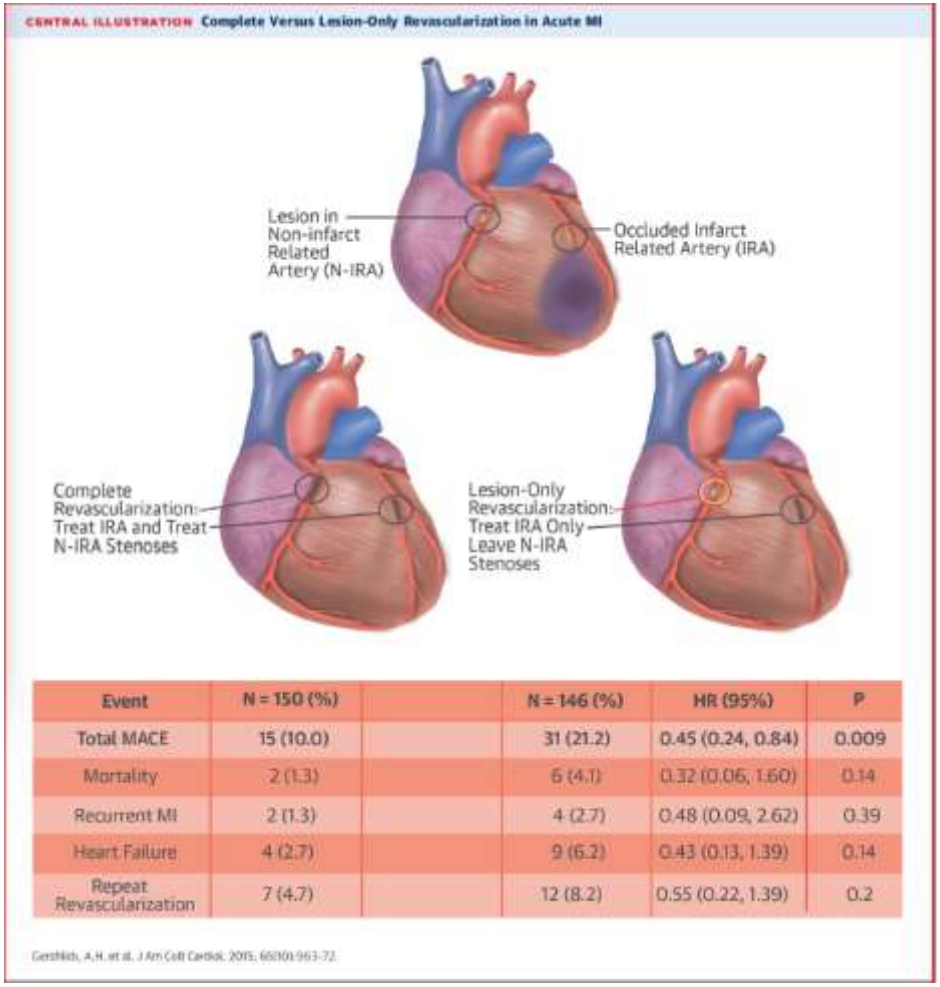
- What was the contribution to the final infarct size of the PCI in the non-infarct related vessel?
- What is the value of PCI in a 50% stenosis in a non-infarct related vessel *at the time of the primary PCI* vs a *staged* PCI in a 90% stenosis in a non-infarct related vessel?
- What was the distribution of stenosis severity left untreated
- Would you participate in a RCT that discouraged a staged PCI for a 90% stenosis in a non-culprit lesion but encouraged a same setting PCI in a non-infarct vessel with a ≥50% stenosis? i.e. clinical equipoise?

Randomized Trial of Complete Versus Lesion-only Revascularization in Patients Undergoing Primary Percutaneous coronary Intervention for STEMI and Multivessel Disease
The CvLPRIT Trial

Gershlick *et al. J Amer Coll Cardiol* 2015;65:963-72

- Open-label RCT comparing complete revascularization (CR) at index admission with treatment of the infarct-related artery only (IRA)
- 296 patients with randomization stratified according to infarct location (anterior/non-anterior) and symptom onset (<3h or >3h) with composite EP of all cause death, recurrent MI, heart failure, and ischemia driven revascularization)
- CR performed at time of PPCI or before discharge
- The primary EP occurred in 10% of CR patients vs 21.2% of IRA patients with no significant reduction in death or MI and a non-significant reduction in all primary EP component as seen

CvLPRIT TRIAL



Event	N = 150 (%)		N = 146 (%)	HR (95%)	P
Total MACE	15 (10.0)		31 (21.2)	0.45 (0.24, 0.84)	0.009
Mortality	2 (1.3)		6 (4.1)	0.32 (0.06, 1.60)	0.14
Recurrent MI	2 (1.3)		4 (2.7)	0.48 (0.09, 2.62)	0.39
Heart Failure	4 (2.7)		9 (6.2)	0.43 (0.13, 1.39)	0.14
Repeat Revascularization	7 (4.7)		12 (8.2)	0.55 (0.22, 1.39)	0.2

Gershlick, A.H. et al. J Am Coll Cardiol. 2015; 65(10):963-72.

CR – 64% at time of PPCI of IRA

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CvLPRIT TRIAL

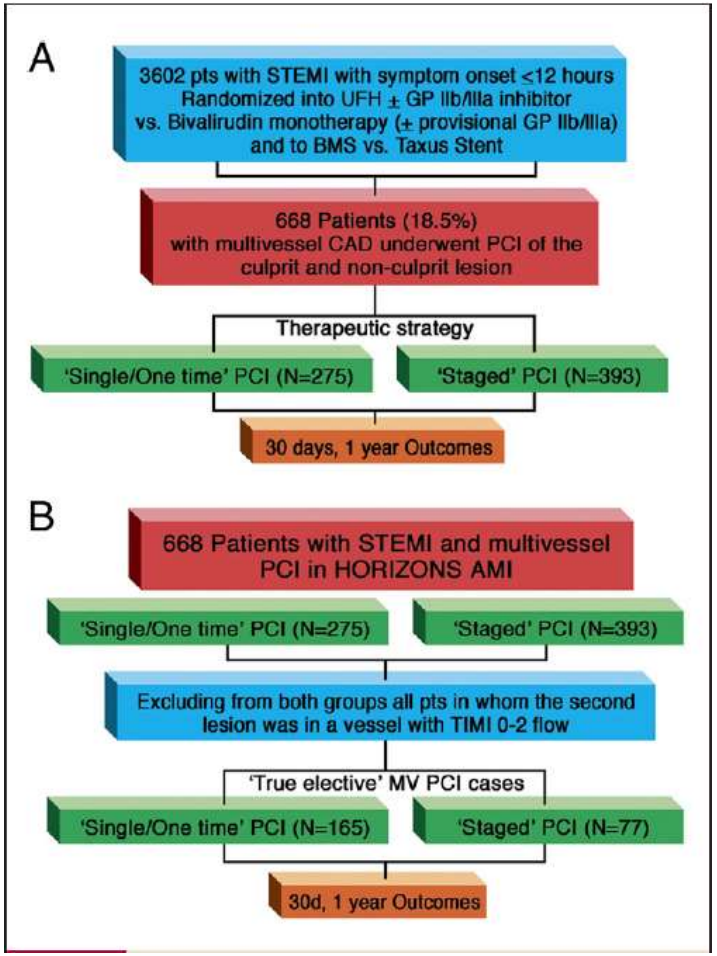
Important Questions/Criticisms

- In the CR group, how did the MVPCI contribute to the peak CNZ levels and the final infarct size? – Were there any significant differences in peak enzyme levels between groups?
- The trial is underpowered with no significant difference between the two groups in the components of the composite EP. As a small study, the study has low statistical power and is vulnerable to the play of chance
- There are few events in the patients which adds to the uncertainty of the results
  - Crossover 5% in IRA only and 7% in CR pts.
  - Lost to f/u 5% in IRA and 7% in CR pts
- CR performed at the time of PCI of IRA in 64% with 36% of patients having "staged CR" – Clearly two different stategies
- Repeat revascularization was for which vessels in the CR group?
- Revascularization is an unreliable measure of benefit in an open-label trial

Kornowski et al. J Amer Coll Cardiol 2011;58:704-711

- Retrospective analysis of prospective, open label, multi-center, RCT of 3602 pts with STEMI & PPCI
- Bivalirudin vs UFH, Taxus vs Express (BMS)
- 668 of 3602 STEMI pts underwent MVPCI in single setting (SS) or staged at operators discretion
- 275 pts (41%) SS MVPCI, 393 pts (59%) Staged
- Pts undergoing MVPCI further stratified by excluding from both groups all pts in whom the second lesion was in a vessel with TIMI flow 0-2 – i.e. emergent nonculprit PCI might have been required

Prognostic Impact of Staged vs "One-Time" MV PCI in Acute MI –Analysis from HORIZONS AMI



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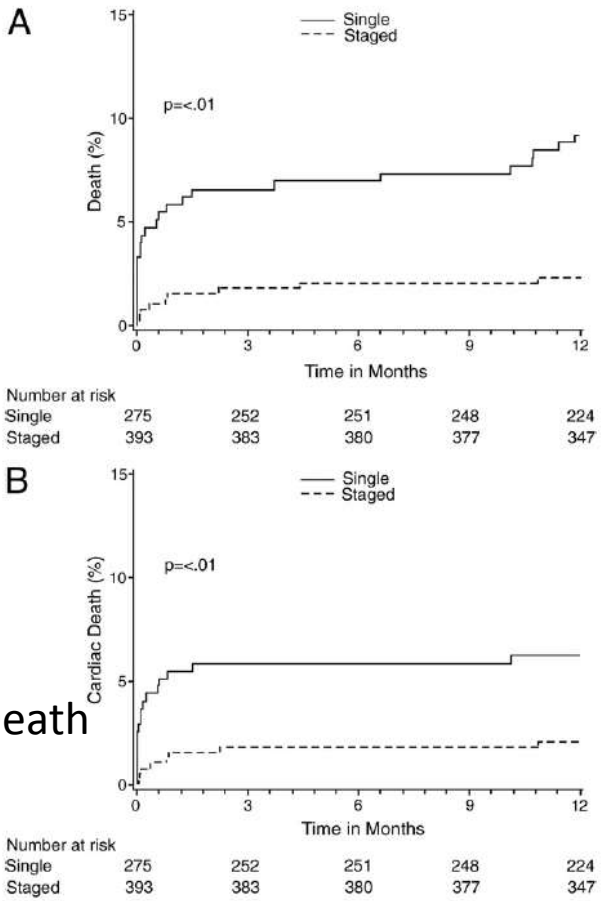
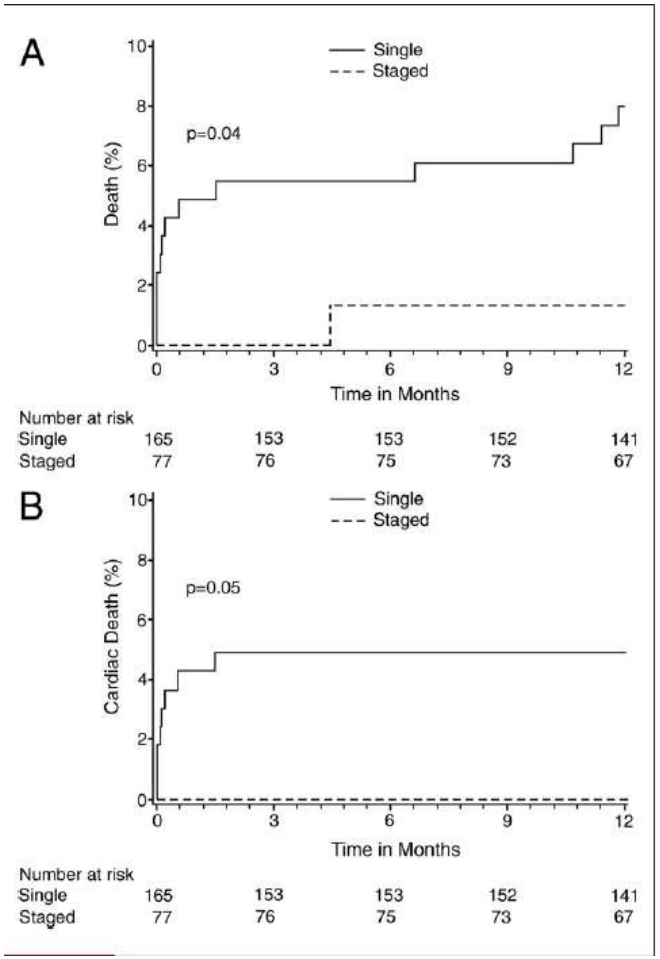
Death

Cardiac Death



Clinical outcome of pts with MVD



Clinical outcomes of True Elective MV PCI pts

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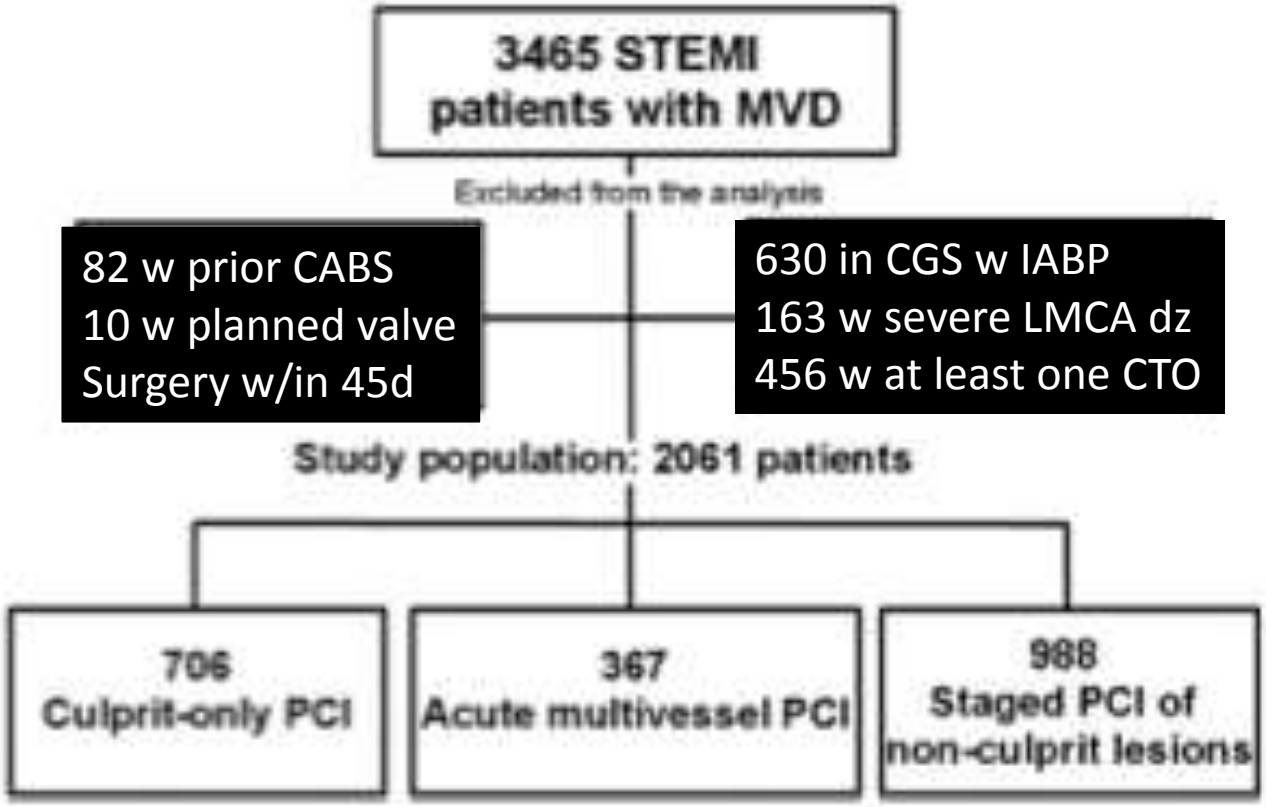
Long-Term Outcome in Patients with ST Segment Elevation Myocardial Infarction and Multivessel Disease Treated with Culprit-Only, Immediate, or Staged Multivessel Percutaneous Revascularization Strategies: Insights from the REAL Registry

Manari *et al. Cath and Cardiovasc Interv* 2014;84:912-922



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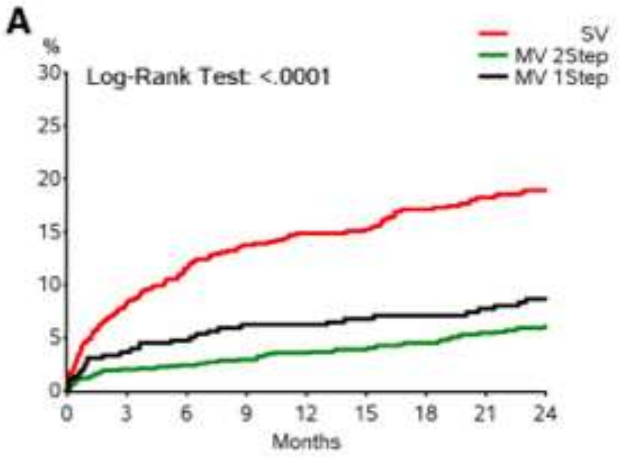
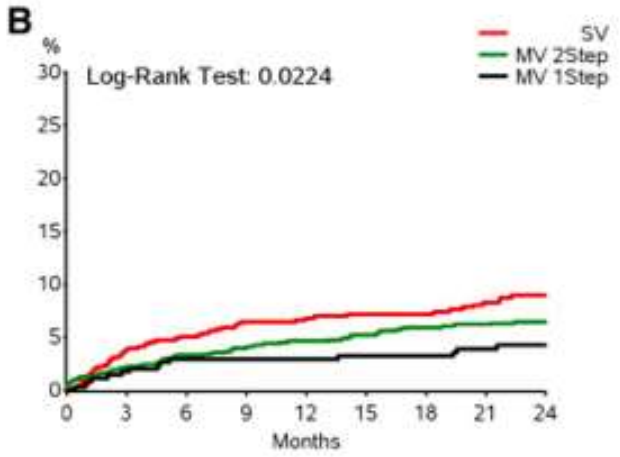
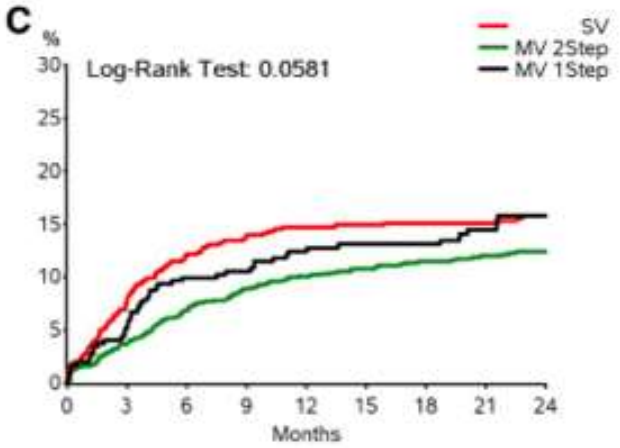
Mortality

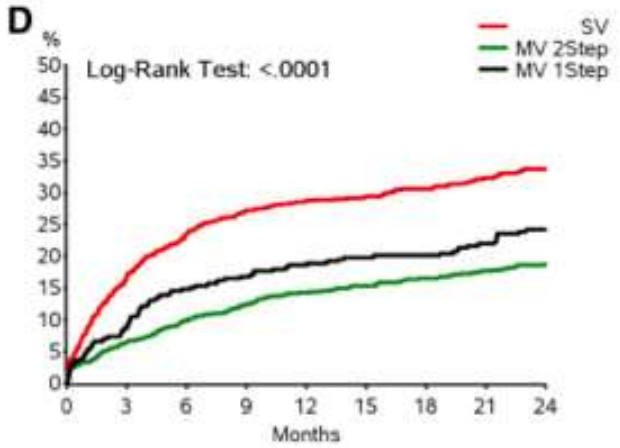




Reinfarction

TVR





MACE

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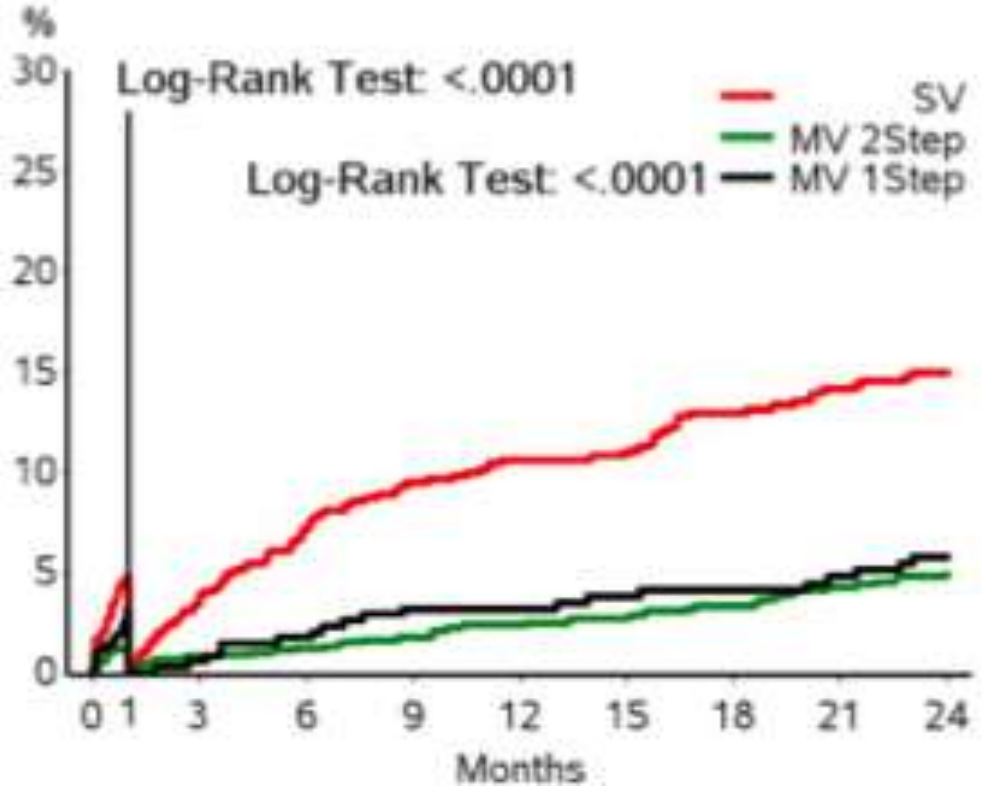
Landmark Analysis of Cumulative Mortality



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Insights from the REAL Registry

- In patients with STEMI and MVD rx'ed with primary PCI in a real world setting, a MV revascularization is associated with better outcomes compared to culprit vessel only PCI
- The treatment of non-IRA at the time of PPCI Resulted in a higher short-term mortality
- Thus, our study support the current guidelines recommendation that in this setting, culprit only primary PCI should be performed at the time of STEMI followed by a staged non-culprit PCI thereafter

Manari *et al. Cath and Cardiovasc Interv* 2014;84:912-922

Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

A Pairwise and Network Meta-Analysis

- In pts with STEMI and MVD should PCI be confined to IRA only or also nonculprit vessels and if NCV's during primary PCI or staged?
- Pairwise and network meta-analyses were performed on 3 strategies for MVD in STEMI
  - Culprit only
  - MV PCI - culprit and ≥ 1 nonculprit
  - Staged PCI, culprit PCI and ≥ 1 non-culprit staged
- Four prospective and 14 retrospective studies involving 40,280 patients were included

Vlaar *et al. J Amer Coll of Cardiol* 2011;58:6920703

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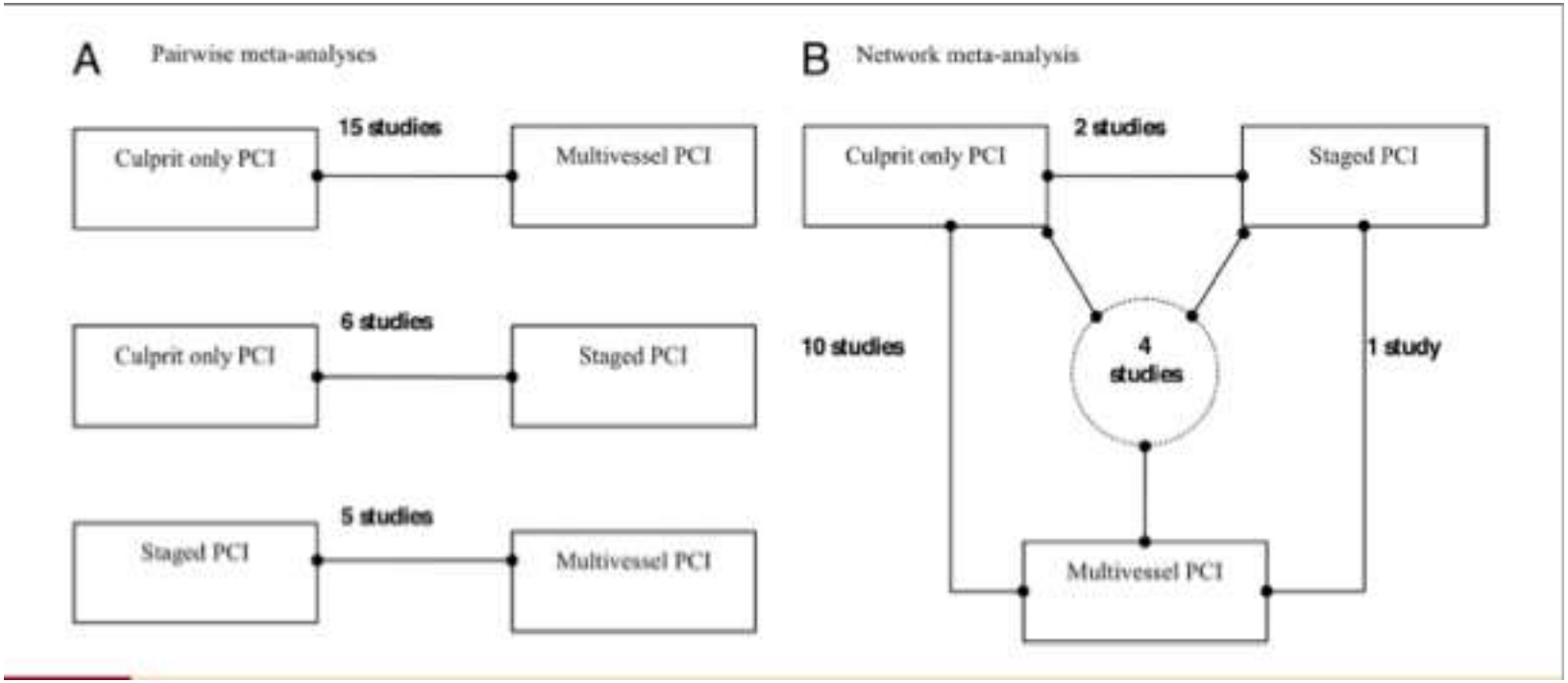
A Pairwise and Network Meta-Analysis

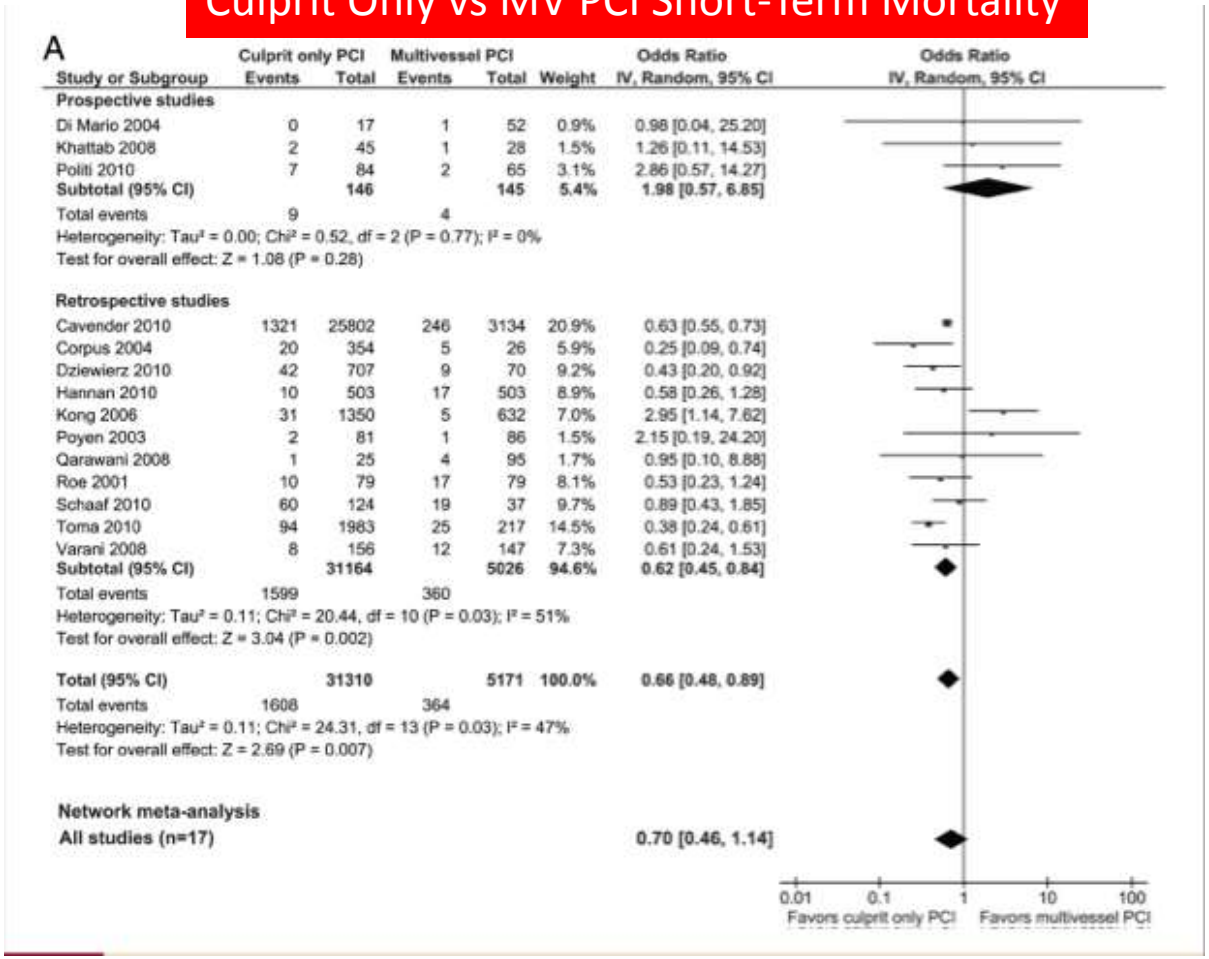


Vlaar *et al. J Amer Coll of Cardiol* 2011;58:692-703

Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

A Pairwise and Network Meta-Analysis

Culprit Only vs MV PCI Short-Term Mortality



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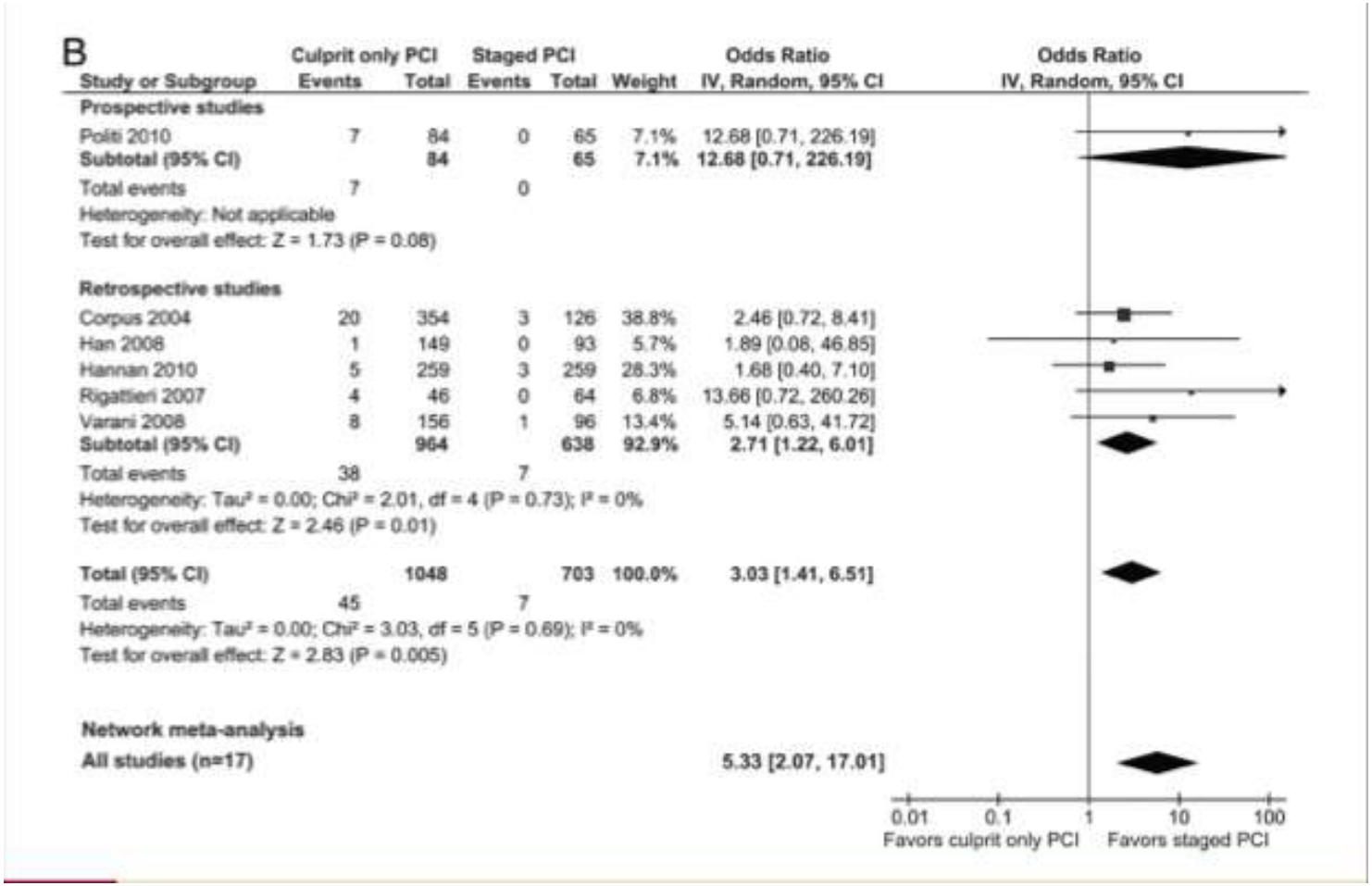

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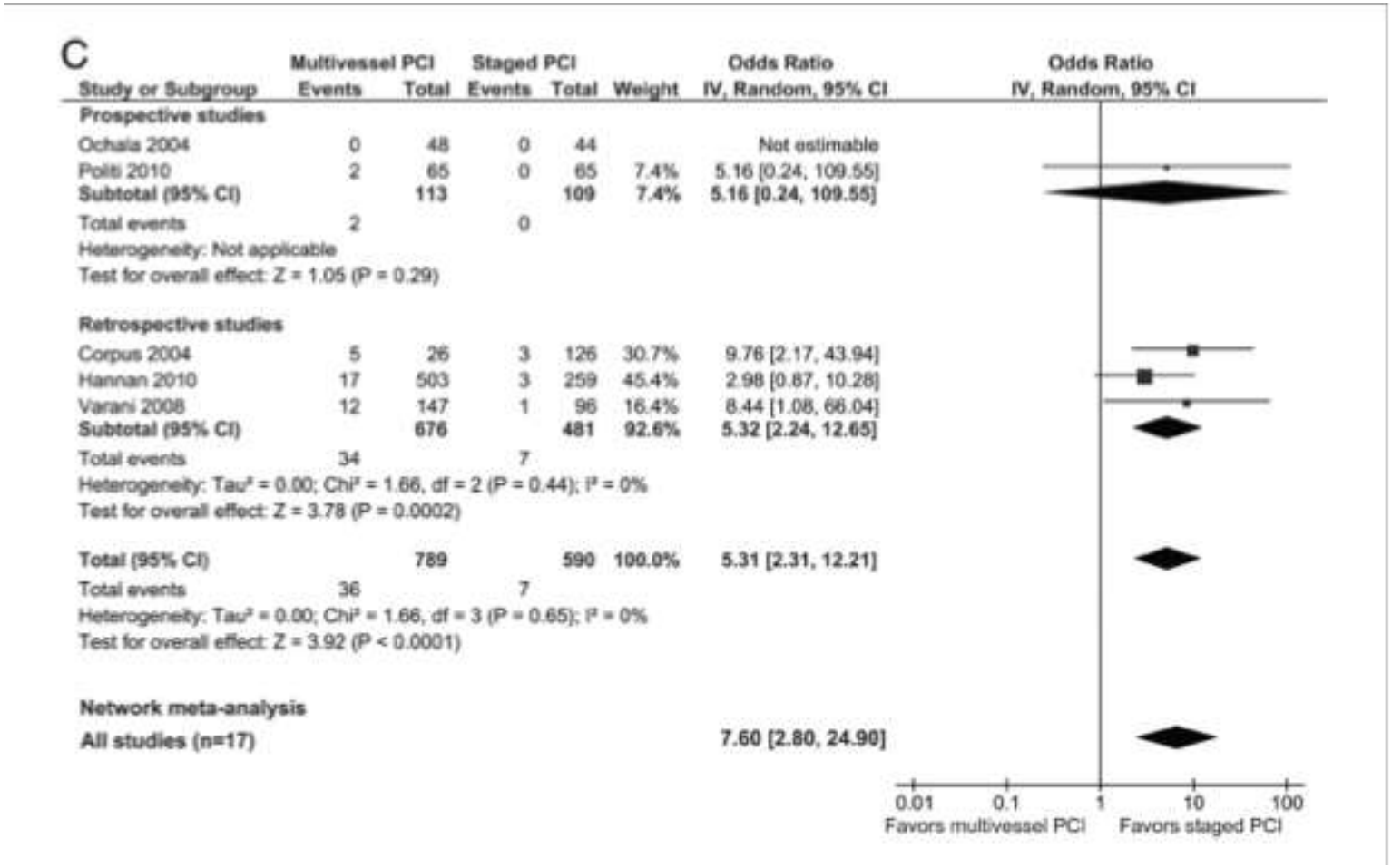
Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

A Pairwise and Network Meta-Analysis

MV PCI vs Staged PCI Short-Term Mortality



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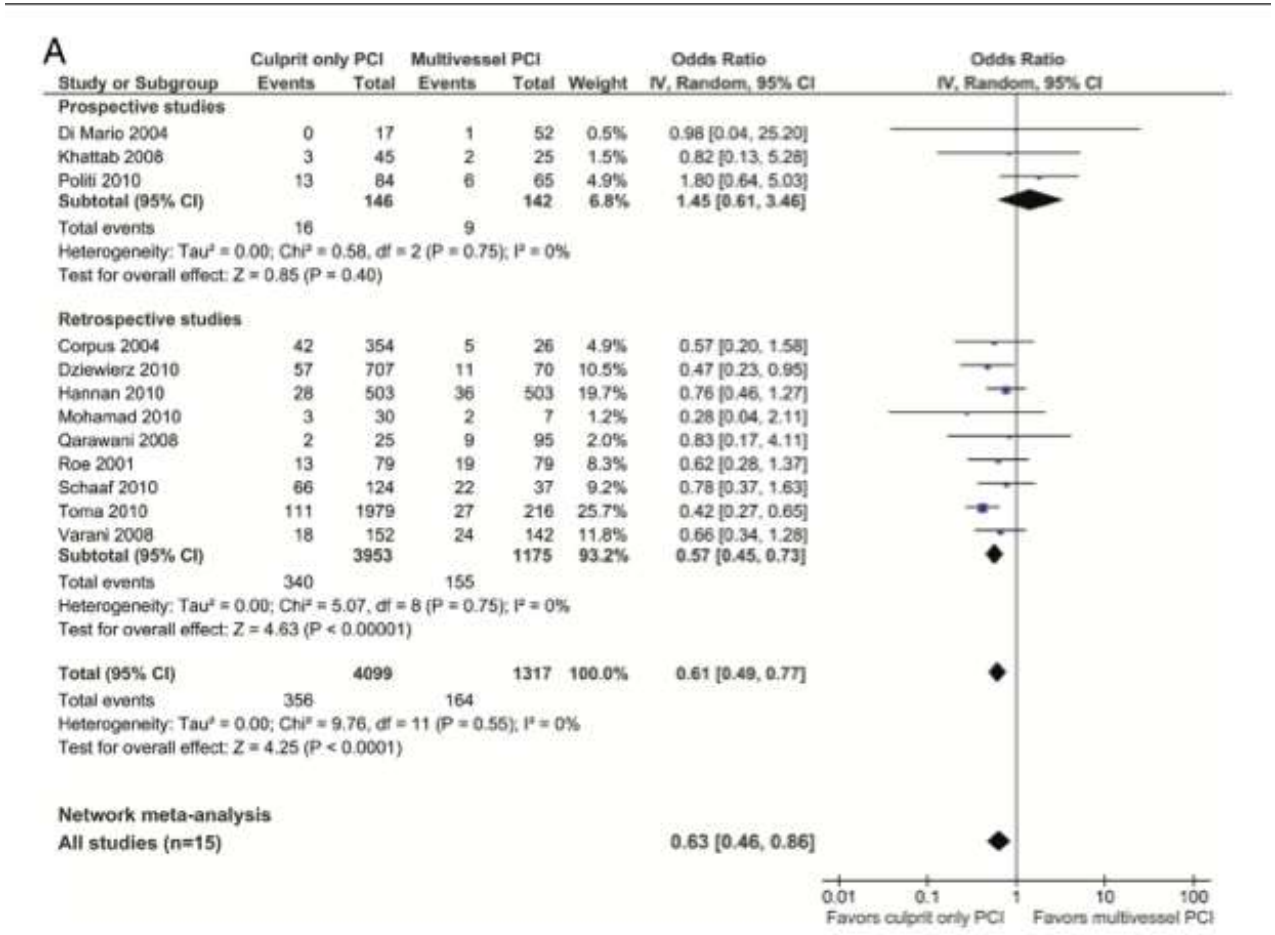
A Pairwise and Network Meta-Analysis

Culprit Only vs MV PCI Long-Term Mortality



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Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

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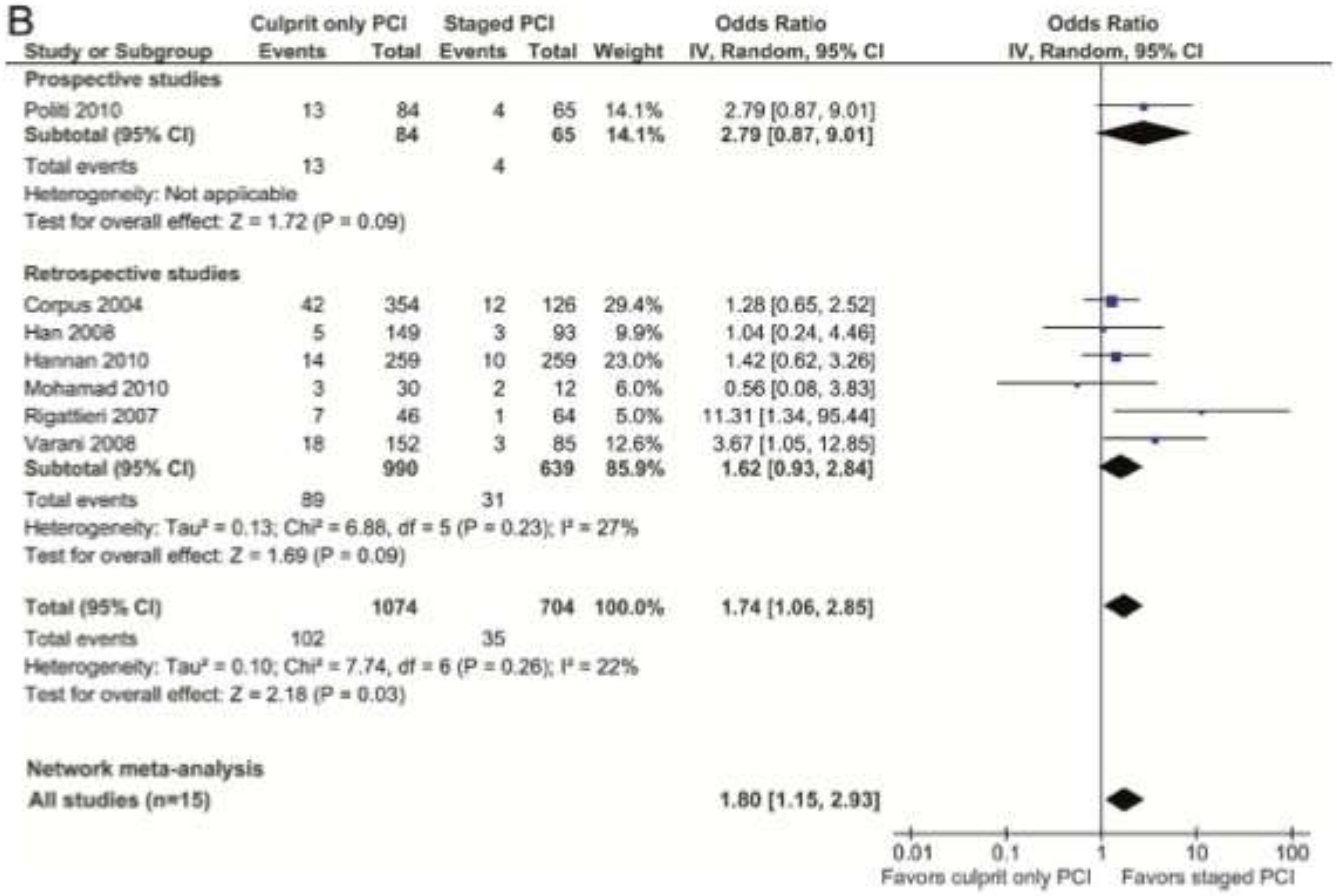
Culprit Only vs Staged PCI Long-Term Mortality



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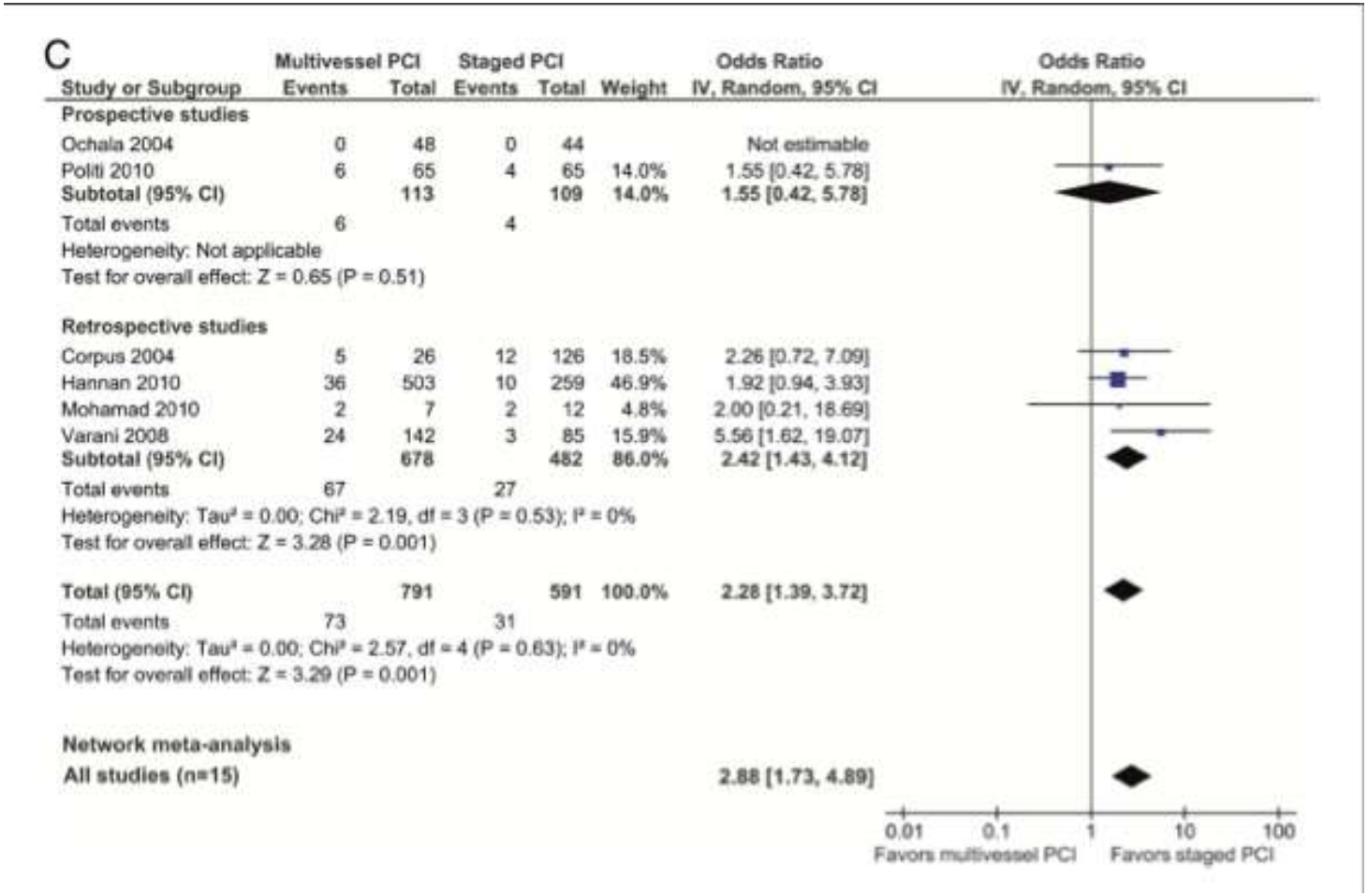
Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

A Pairwise and Network Meta-Analysis

MV PCI vs Staged PCI Long-Term Mortality



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Culprit Vessel Only vs MV and Staged PCI for MVD in Patients Presenting with STEMI

A Pairwise and Network Meta-Analysis

- Pairwise meta-analyses demonstrated that ***staged PCI*** was associated with **lower short- and long-term mortality** as compared to culprit PCI and MV PCI
- **MV PCI** was associated with the **highest mortality** rates at both short and long-term f/u
- This meta-analysis supports current guidelines **discouraging performance of MV primary PCI for STEMI.**
- When **significant nonculprit vessel** lesions are suitable for PCI, they should be treated during **staged** procedures

Vlaar *et al. J Amer Coll of Cardiol* 2011;58:692-703

Multivessel vs Culprit Only PCI in STEMI

Comments/Perspective

- Further large scale RCT's to address the impact of complete revascularization on hard end points (death and recurrent MI) are required – await the results of ongoing COMPLETE Trial
- FFR estimation of nonculprit lesion *severity* should be considered particularly if MV PCI done in STEMI (staged) setting
- Until there is a definitive large randomized trial, a deferred angioplasty strategy of non-culprit lesions in STEMI should be the standard of care in non-shock patients
- Nonetheless, there will be exceptions where with the exercise of a physician's best judgment MV PCI in the setting of STEMI may be required in an individual patient