Composite Endpoints in Renal Transplantation

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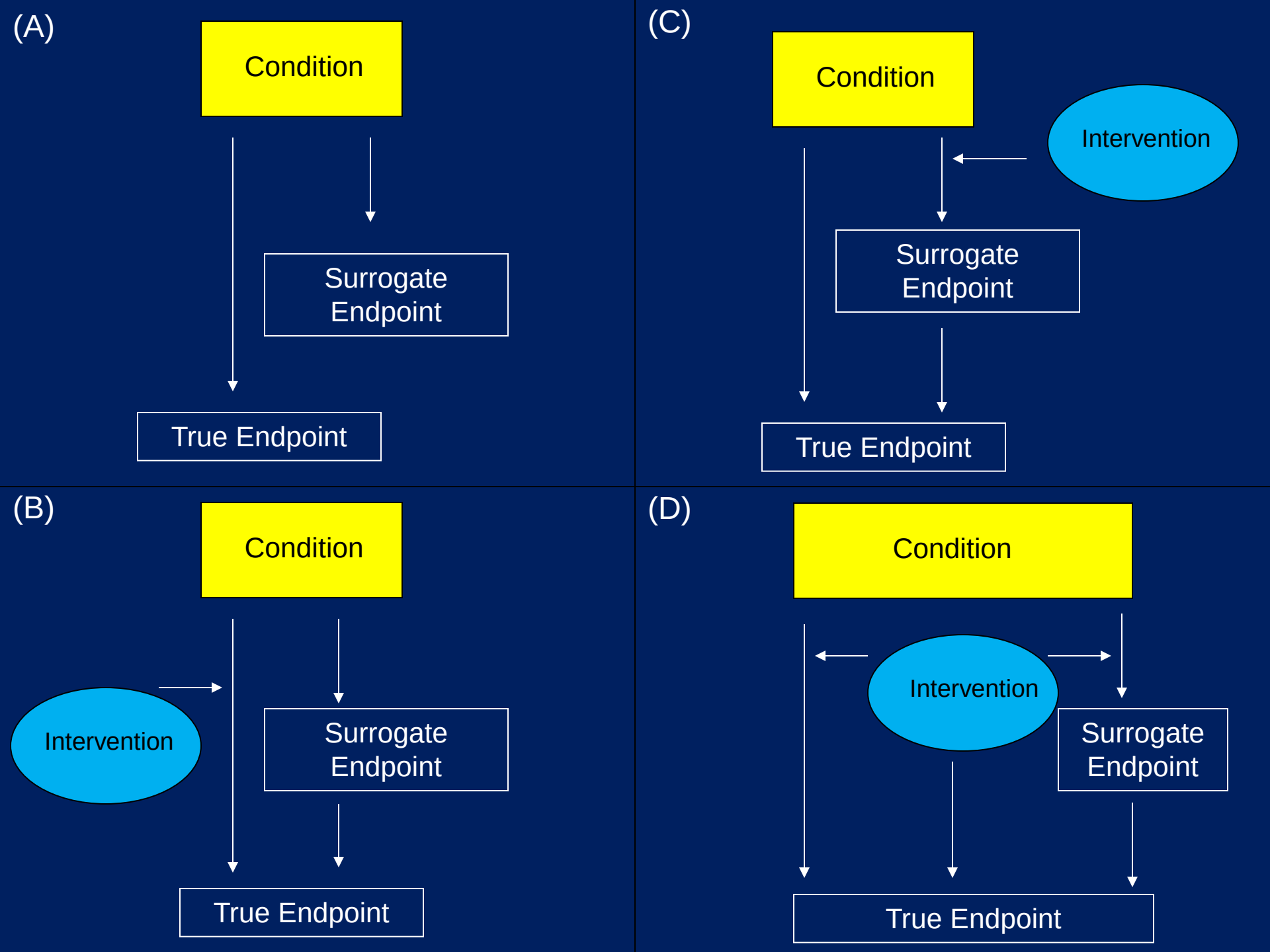
Prentice Criteria

1) The treatment of intervention must affect the surrogate endpoint(s)

2) The treatment or intervention must affect the true endpoint

3) The association of the surrogate endpoint and the true endpoint must be consistent between the treatment or intervention

4) There is an association between the surrogate and the true endpoints


(A)
Condition
Surrogate Endpoint
True Endpoint
(C)
Condition
Intervention
Surrogate Endpoint
True Endpoint
(B)
Condition
Intervention
Surrogate Endpoint
True Endpoint
(D)
Condition
Intervention
Surrogate Endpoint
True Endpoint

The Value of Composite Endpoints

- Typically to increase statistical power and limit resources necessary if a therapy is likely to have similar effects
- Incorporate multiple clinically relevant events which may be ignored with a single endpoint
- Also allows reporting of individual components for prospective hypothesis generation
- Not ‘ignoring’ primary endpoints of interest (e.g. death) even if rare
- Concern of competing risks with surrogate endpoint alone

Limitations of Composite Endpoints

- May combine events with highly differential impact on patient outcomes
  - possibly with different perceptions by trialists and patients (impact of patient preferences)
- Depending on selection of endpoints, may be 'overpowered' by specific events or dilute effects
- Primary endpoints (e.g. death) may have incidence in the direction opposite of the composite endpoint
- Potential difficulties with interpretation of composite outcome

The Opticept Trial: Treatment Failure at 12 Months

	Group A MMF_{CC}/CNI_{RL} N=243	Group B MMF_{CC}/CNI_{SL} N=237	Group C MMF_{FD}/CNI_{SL} N=240
Treatment Failure	55 (22.6%)*	67 (28.3%)	67 (27.9%)
Reason for Treatment Failure			
Biopsy-proven Acute Rejection	15 (6.2%)	23 (9.7%)	23 (9.6%)
Graft Loss	5 (2.1%)	4 (1.7%)	4 (1.7%)
Death	4 (1.6%)	2 (0.8%)	6 (2.5%)
Lost to Follow-up or Discontinued	15 (6.2%)	18 (7.6%)	22 (9.2%)
Withdrew Consent	16 (6.6%)	20 (8.4%)	12 (5.0%)

Considering Weighted Composite Endpoints

- Benefit is to apply appropriate ‘value’ on given clinical event
- May decrease power from ‘all-cause’ composite but reduce variation if treatment effects are in same direction
- Big question is often how to weight and does the weighting apply equally by therapy, population, etc.

Case Examples: Potential 1-year Endpoints in National Transplant Registry Data for Kidney Recipients

- Dialysis within first week (DGF)
- 1-year treatment for acute rejection
- 1-year GFR
- Slope in GFR 6 months- 12 months
- Treatment of BK Virus
- Malignancies
- Hospitalizations
- Graft Loss
- Death

In addition, claims data has information used to estimate incidence of:

- Cardiac events
- New-onset diabetes
- Infections
- Etc..

Case Examples:
Endpoints in National Registry Data 2009-2013 (among adult primary kidney transplant recipients)

Endpoint	Incidence (mean) at one-year
DGF	16.7%
1-year AR	8.0%
1-year GFR	64.2 (sd=27.4) mL/min/1.72m^2
Change 6-mo to 12-mo GFR	-0.3 (sd=12.6) mL/min/1.72m^2
Treatment for BK Virus	5.7%
Malignancy	1.2%
Hospitalization	35.3%
Graft Loss	2.7%
Death	2.7%

Case Examples: Association of Endpoints in National Registry Data with 5 year death

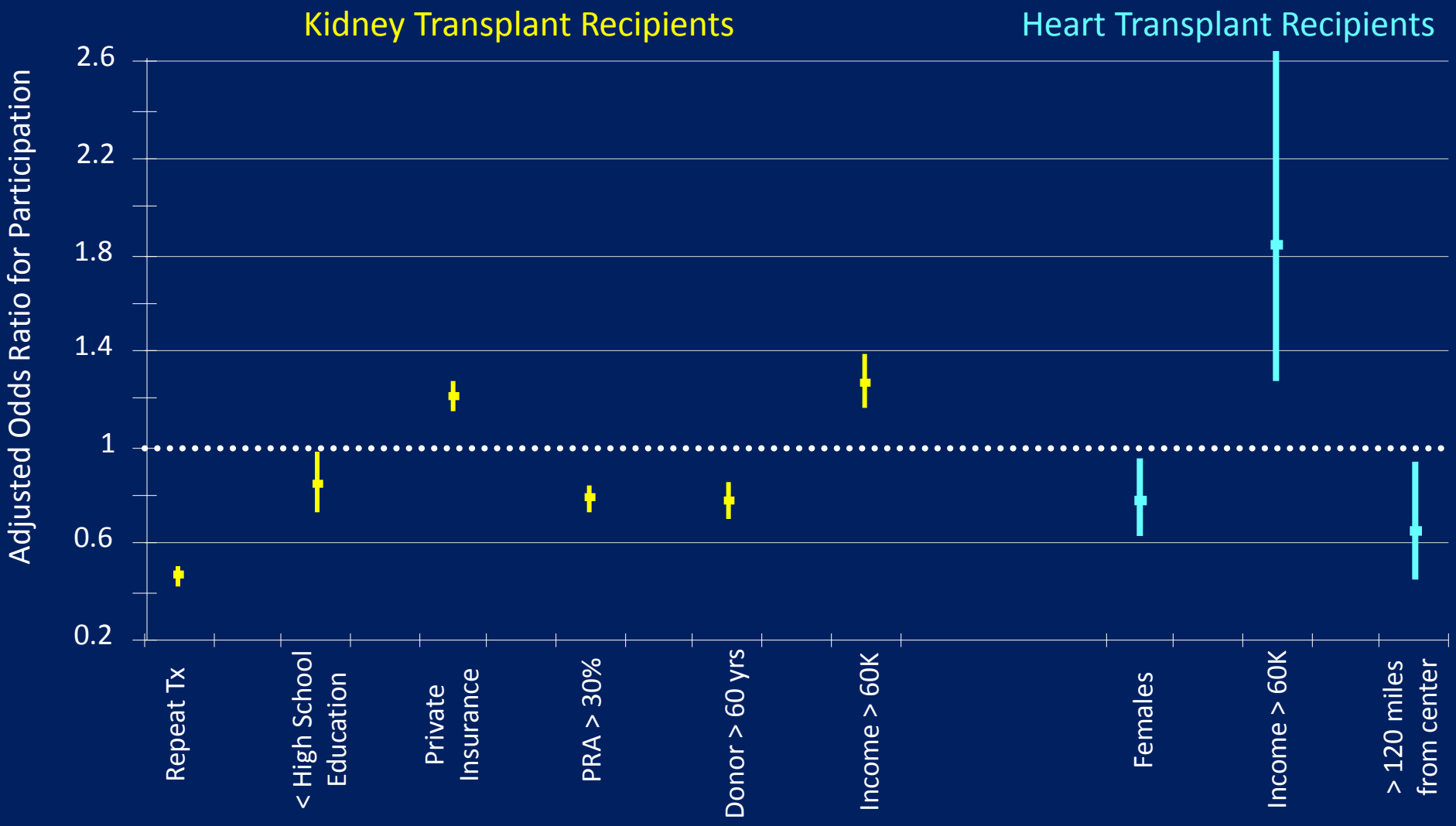
Event at 1 year post-transplant	5-year conditional survival with event	5-year conditional survival without event
DGF	86%	92%
1-year AR	87%	92%
1-year GFR	OR=0.98 per mL/min	
Delta GFR (6-12 mo)	OR=1.01 per decreased mL/min	
Malignancy	80%	91%
Hospitalization	88%	94%
Graft Loss	64%	89%

Case Examples:

Multivariable Association of Endpoints in National Registry Data with 5 year death

1-year clinical endpoint	5-year adjusted hazard for death
DGF	AHR=1.19, 1.06-1.32
1-year AR	AHR=1.38, 1.21-1.57
1-year GFR	AHR=0.94, 0.92-0.97 per 10 mL/min
Delta GFR	AHR=1.01, 1.01-1.02 per mL/min
Tx for BK Virus	AHR=0.99, 0.84-1.17
Malignancy	AHR=2.28, 1.83-2.83
Hospitalization	AHR=1.73, 1.58-1.90

Participation in Research



Source: Schold et al, Transplantation

Summary and Conclusions

- Composite endpoints should be considered for trials in transplantation given potential to improve efficiencies and incorporate multiple pathways of therapeutic effects
- Weighted composite endpoints may further advance the specificity of evaluating interventions
- National data may be used to inform trial development as well as heterogeneity of incidence by center
- Careful consideration of external generalizability of effects based on patient participation as well as selectively including patients more likely to occur events to improve efficiencies