Summary of results from pre-workshop assignment: In vivo practices

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April 14, 2014

Outline

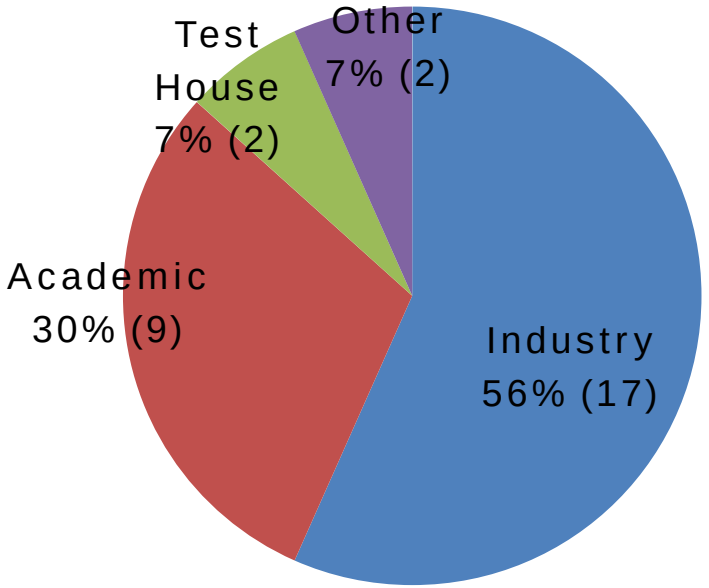
- Background on pre-workshop homework assignment
- Summary of in vivo results:
  - Why conduct an in vivo test?
  - Ideas to optimize the animal models
- Conclusions

Views expressed are those of the non-FDA pre-workshop participants.

Background on pre-workshop homework assignment

- Distributed on Nov. 7, 2013
- Solicit information on current practices for thrombogenicity testing
- Feedback was used to:
  - Inform agenda topics
  - Inform panel discussions

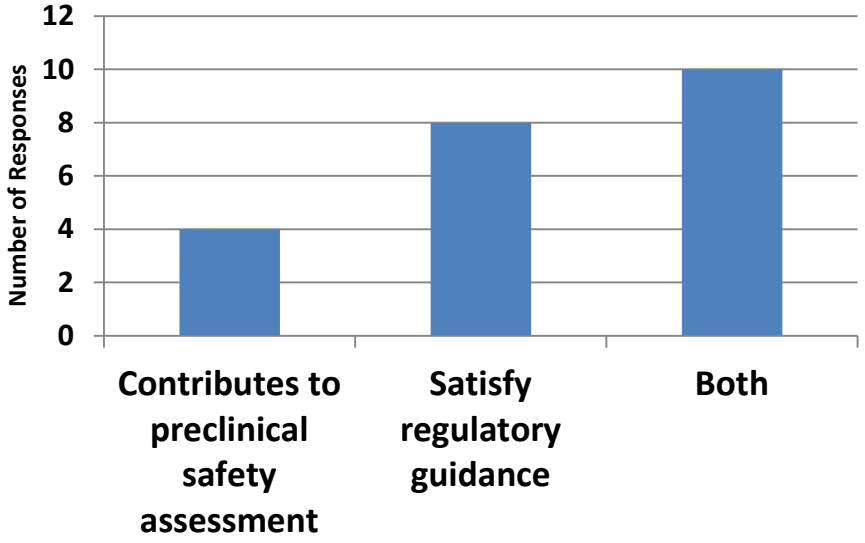
30 responders



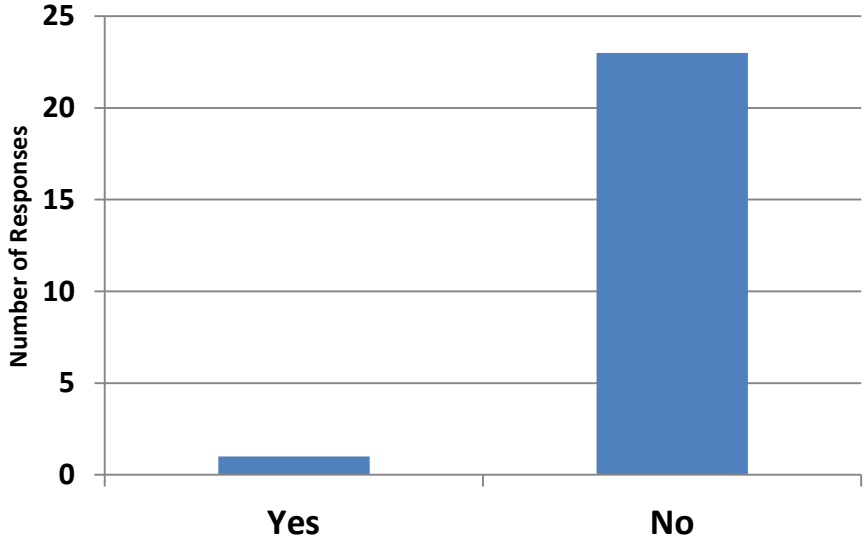
In vivo practices

Why conduct in vivo thrombogenicity testing?

Q6b: For what reason do you conduct in vivo thrombogenicity? (22 responses)



Q13a: Is the 4hr unheparinized canine model clinically relevant? (24 responses)



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How can we reduce in vivo variability and increase predictivity?

Factor	# of responses*
Use anticoagulant (if indicated)	5
Use longer duration (per indication)	5
Use shorter duration (per indication)	5
Use clinically relevant vessel size	4
Use within-animal controls	4
Use arterial placement (if indicated)	2
Use fluoroscopy/ultrasound	2
Standardize fluid/ventilatory support	2

**Summary of feedback that received > 1 response*

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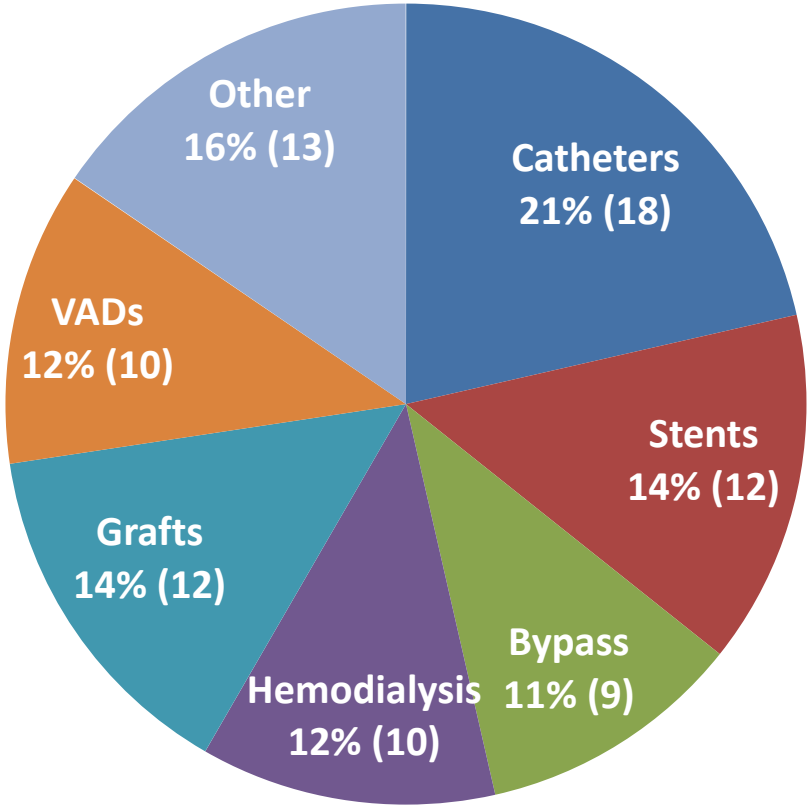
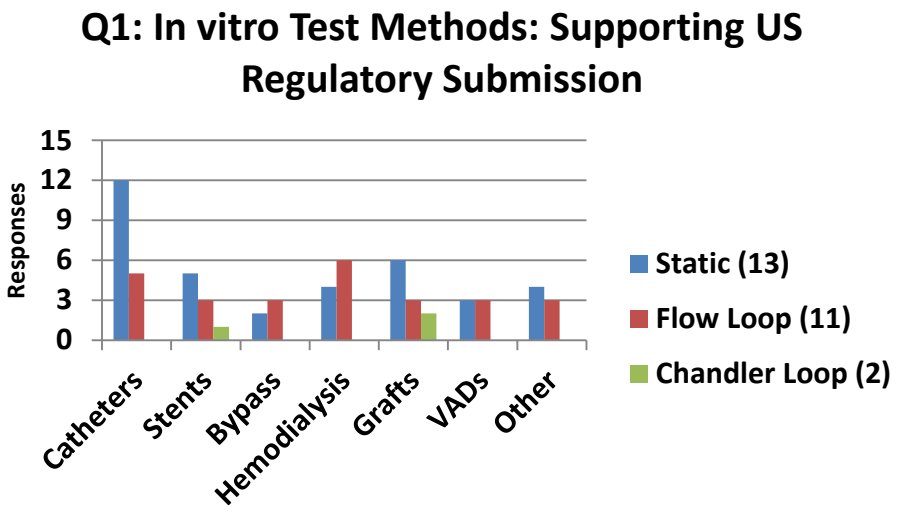
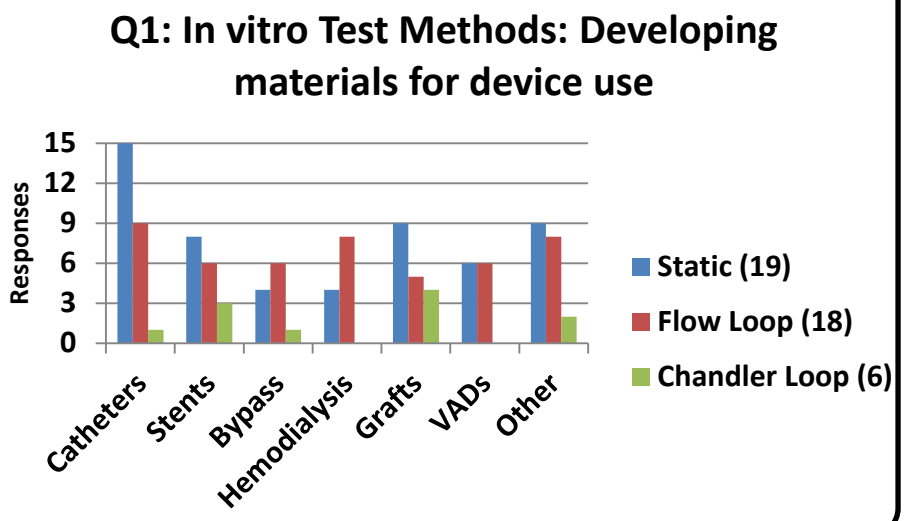
Response demographics: device type

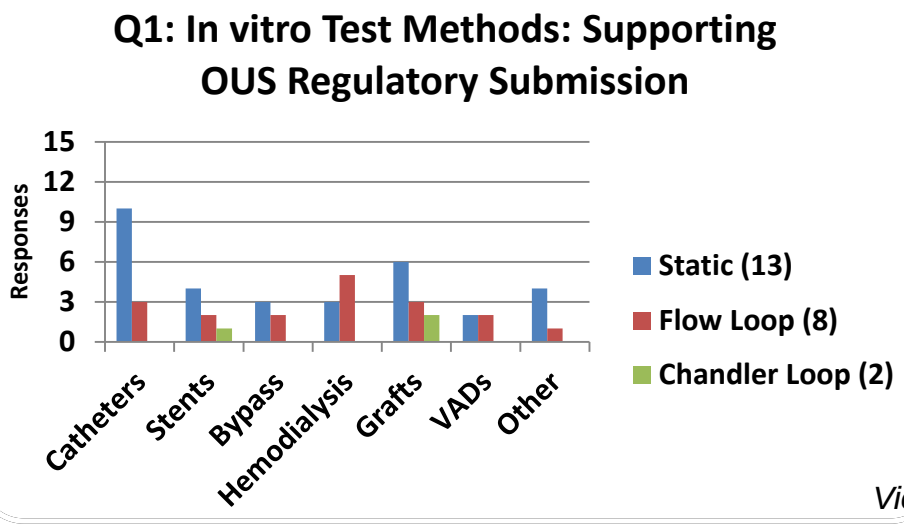


n=84

In vitro assessment strategies







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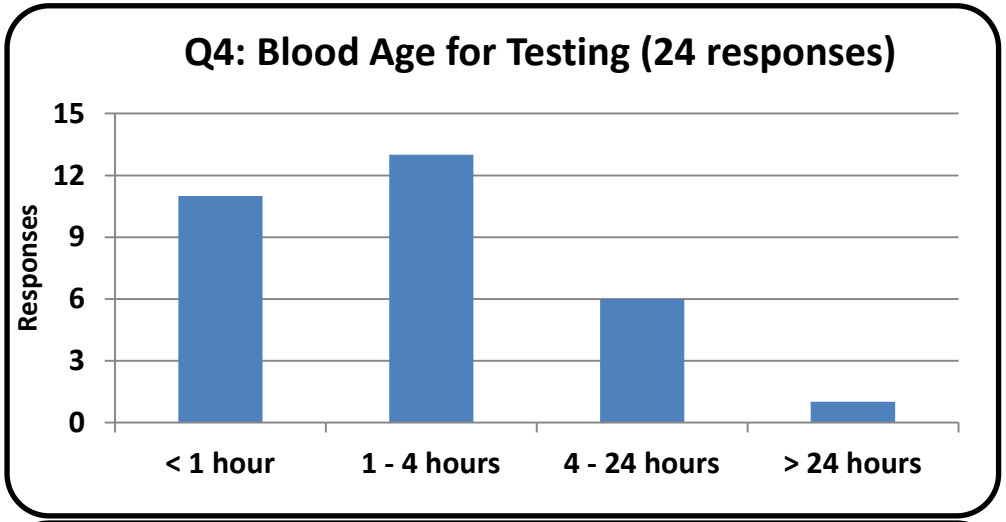
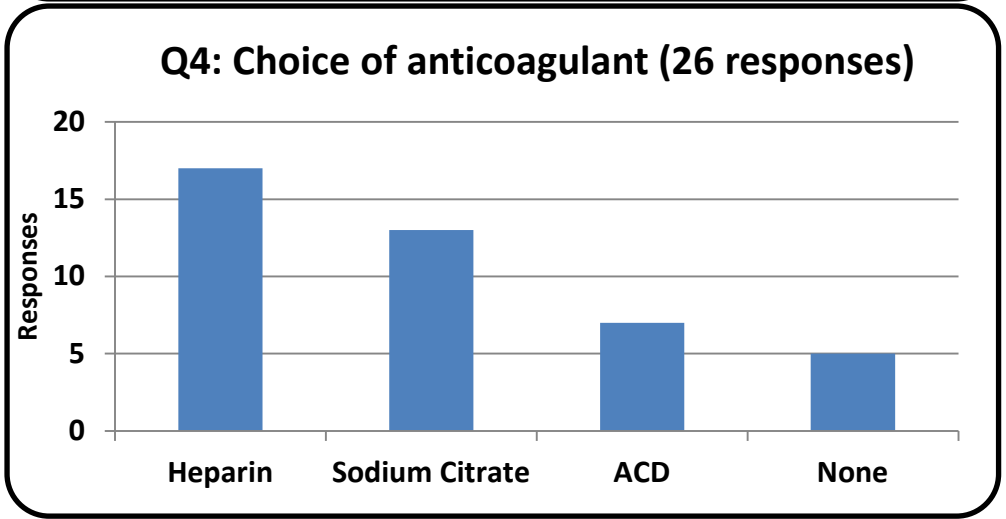
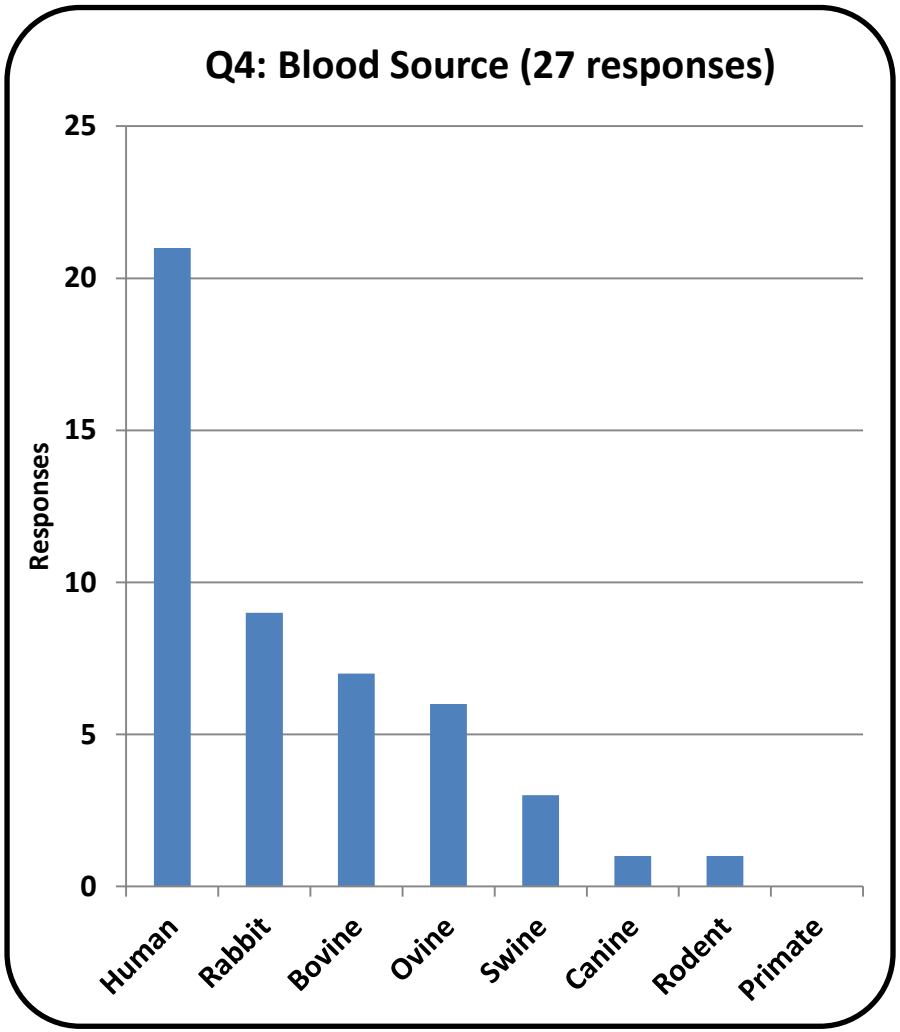
In vitro methods:

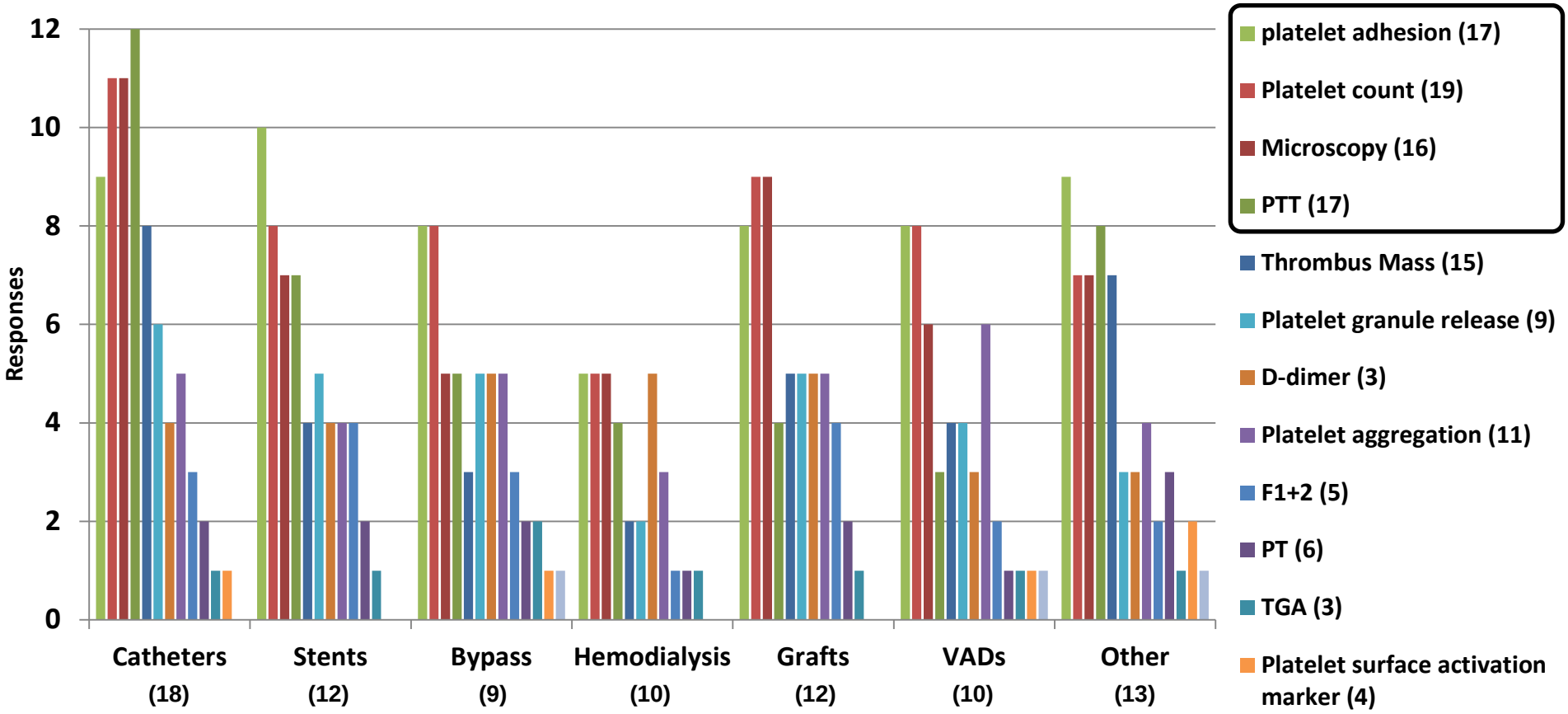
blood age, anticoagulant, source







Most common in vitro endpoints



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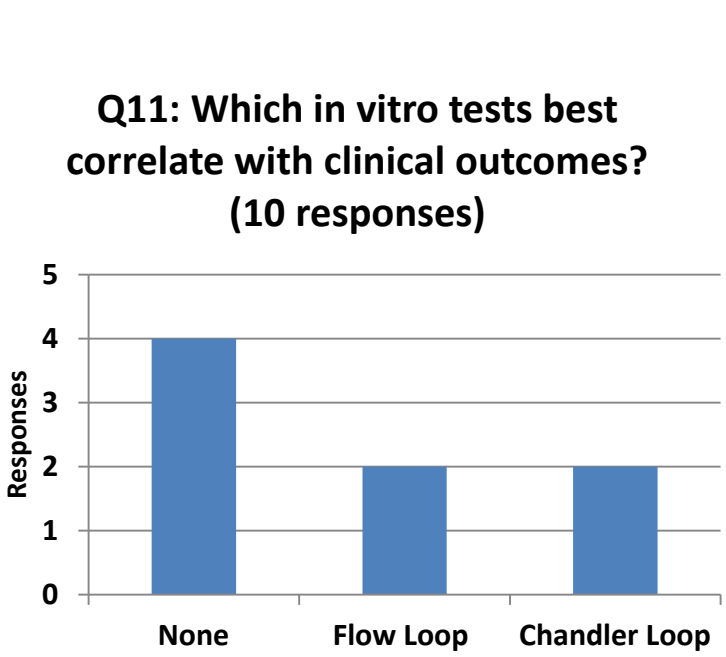
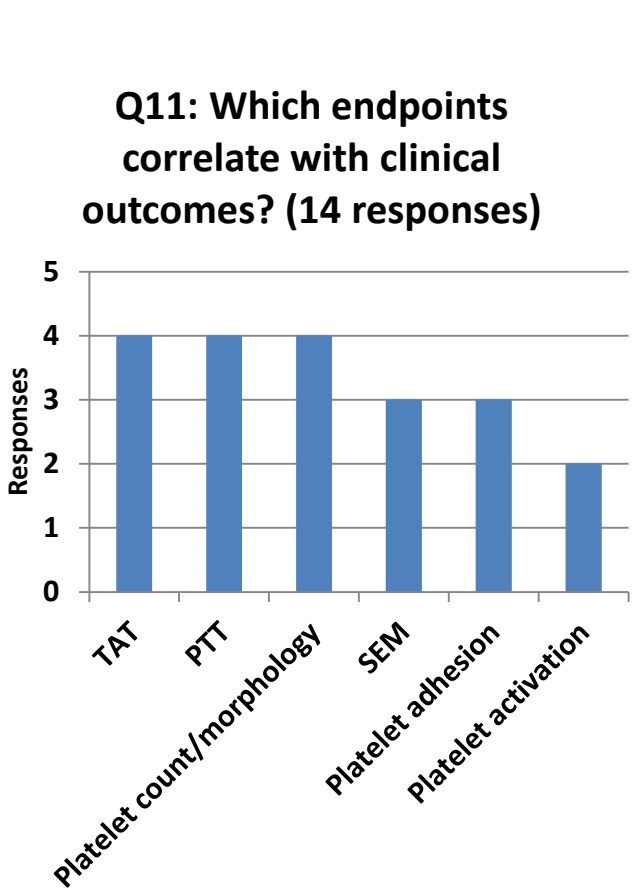
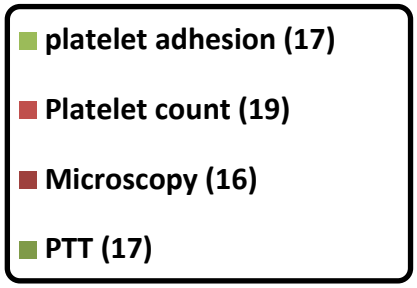
Correlation of in vitro tests/endpoints with clinical outcomes







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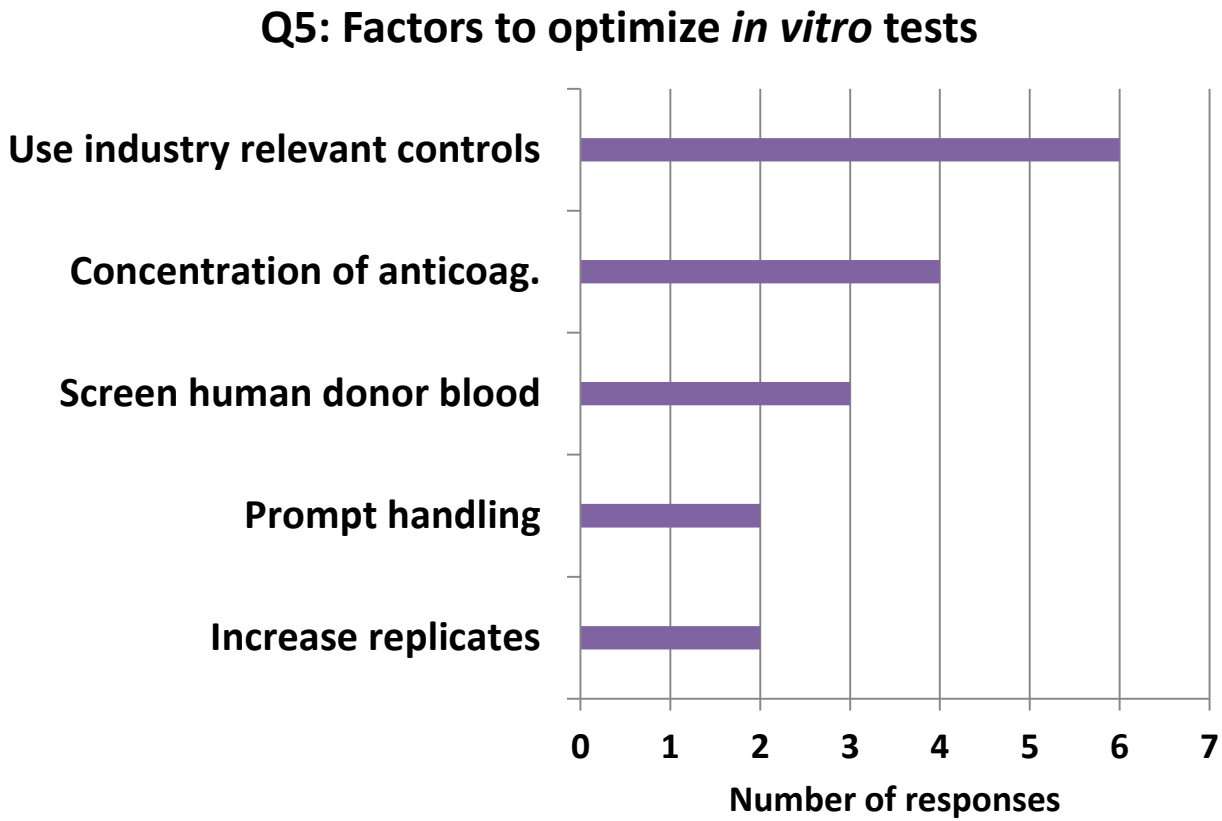
How can we reduce variability and increase predictivity?



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Review

Most common in vitro testing strategy:

- Design: Static or Flow Loop
- Blood: Sourced from humans, anticoagulated with heparin or sodium citrate, and used for testing within 4 hrs
- Endpoint: PTT, microscopy, platelet count, and platelet adhesion

Summary of results from pre-workshop assignment: Device specific considerations

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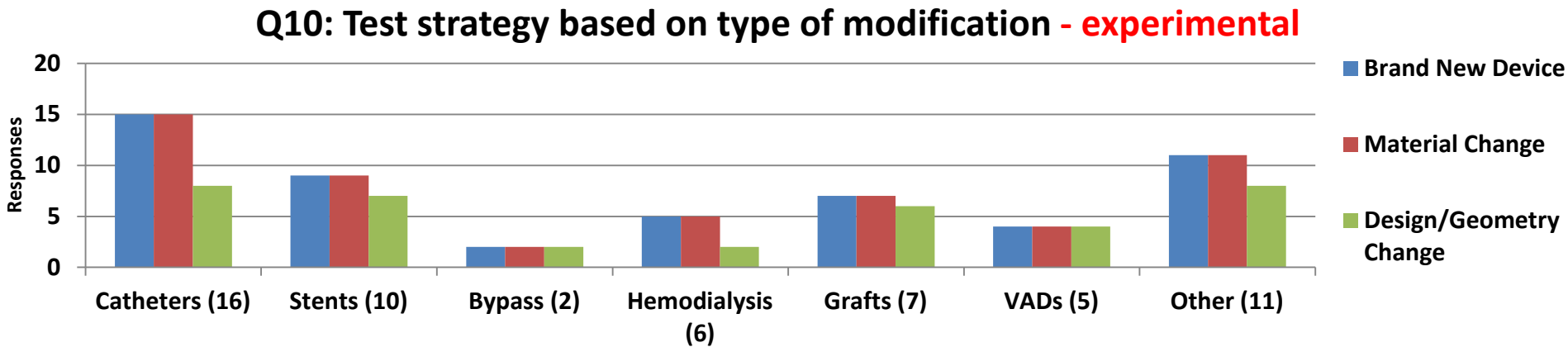
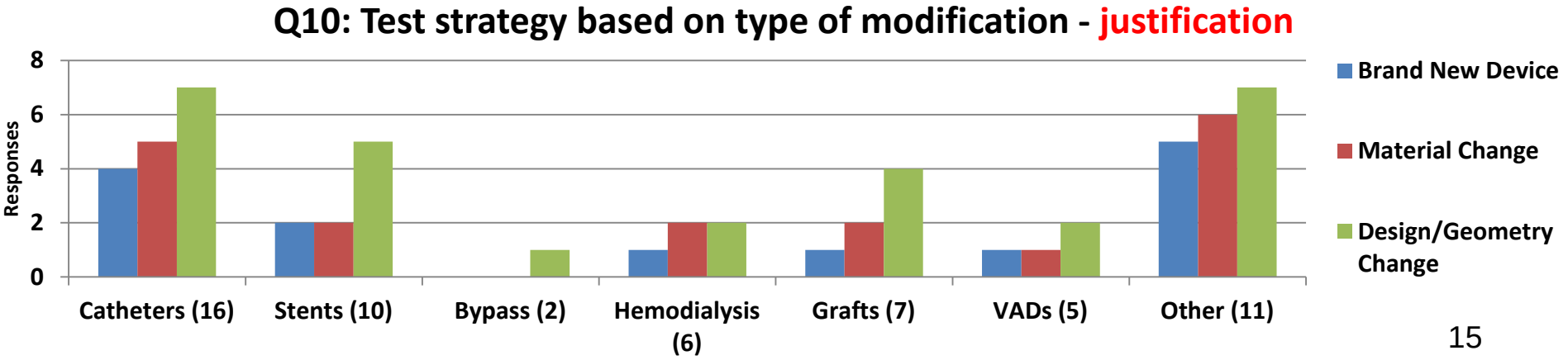
Regulatory test strategy stratified by device type





Device specific considerations

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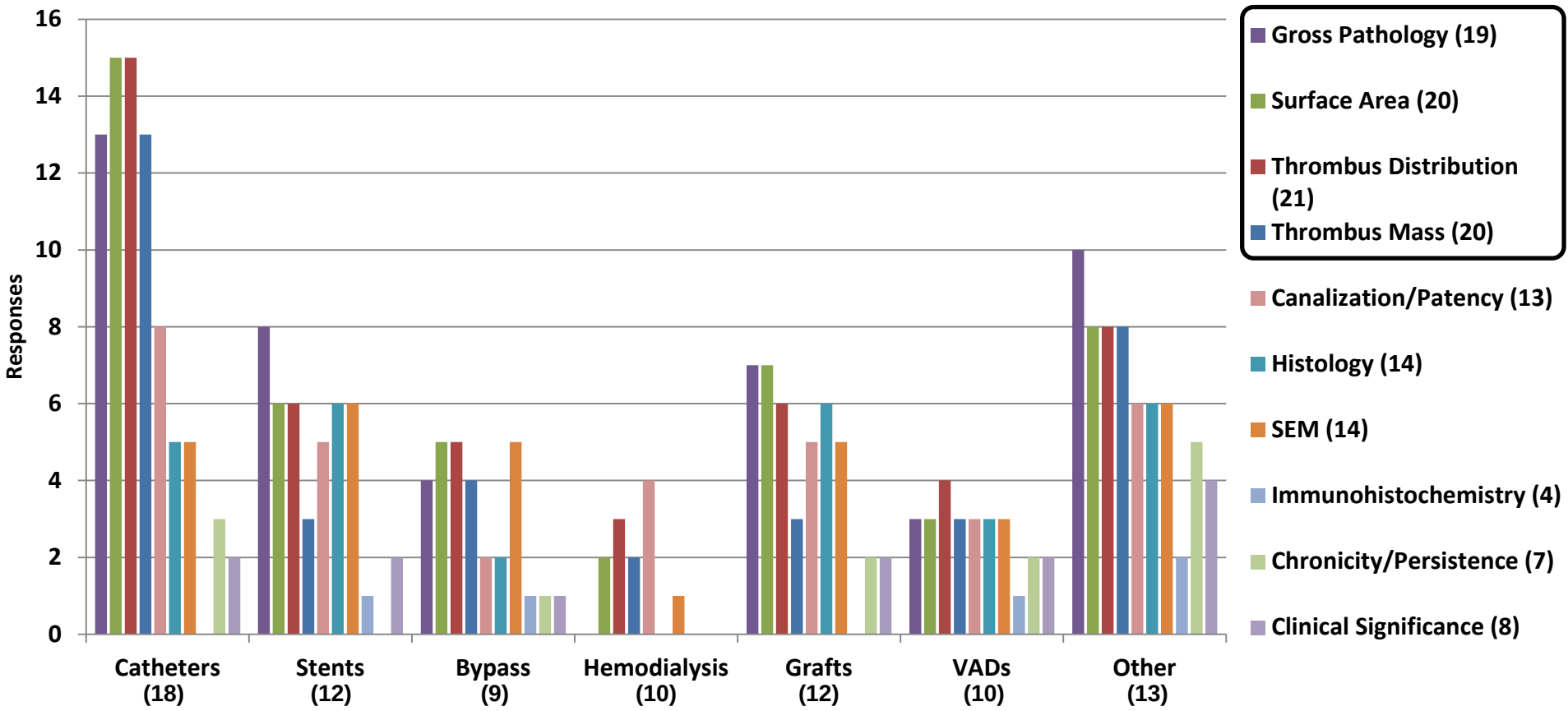
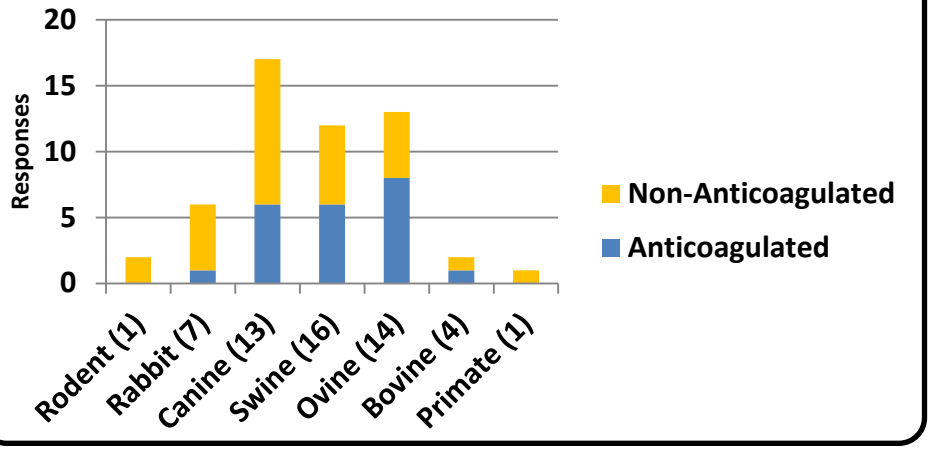
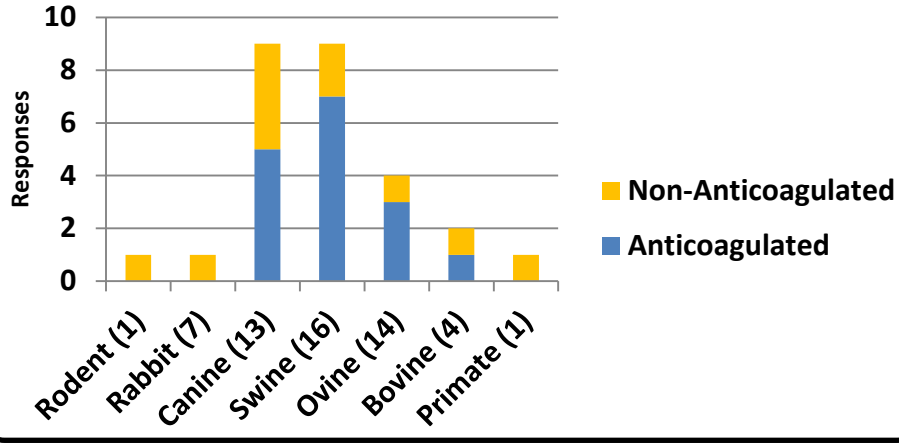
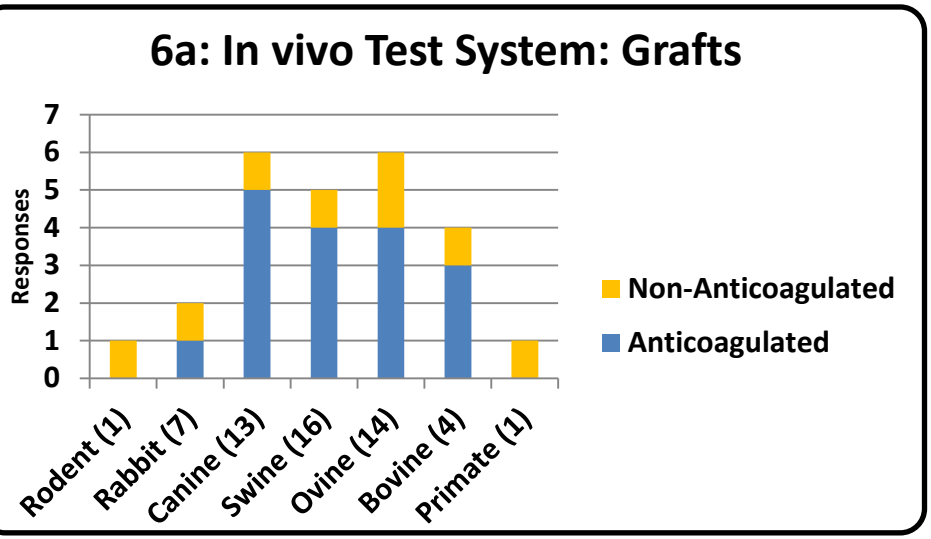
Most common *in vivo* endpoints

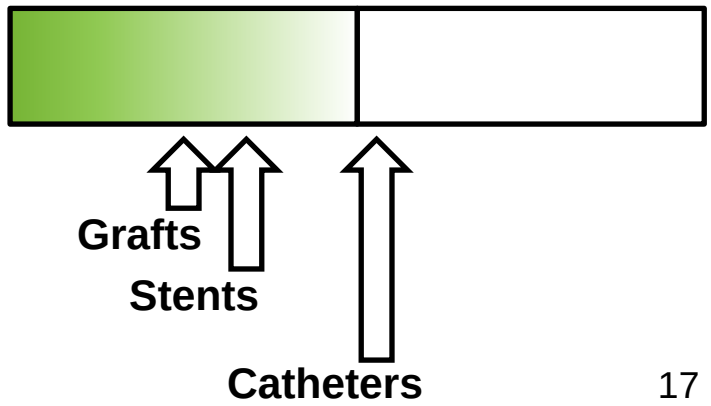


In vivo model system: device type









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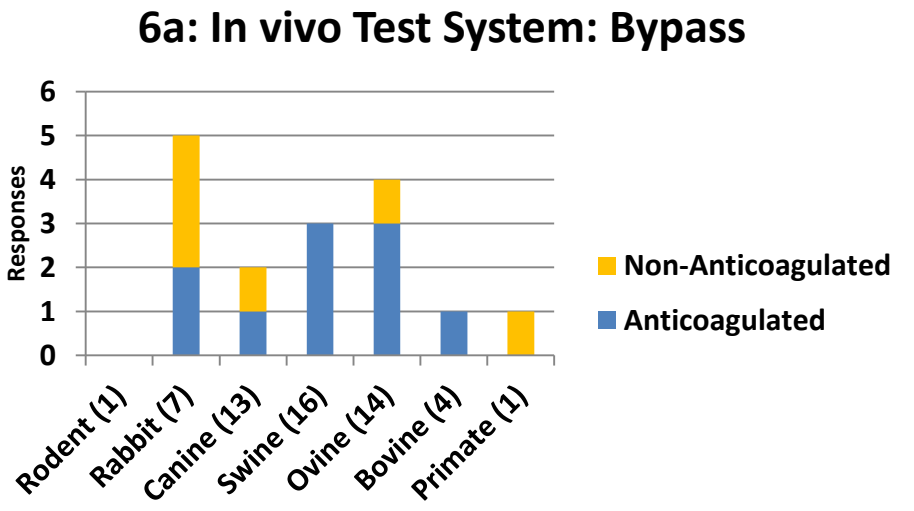
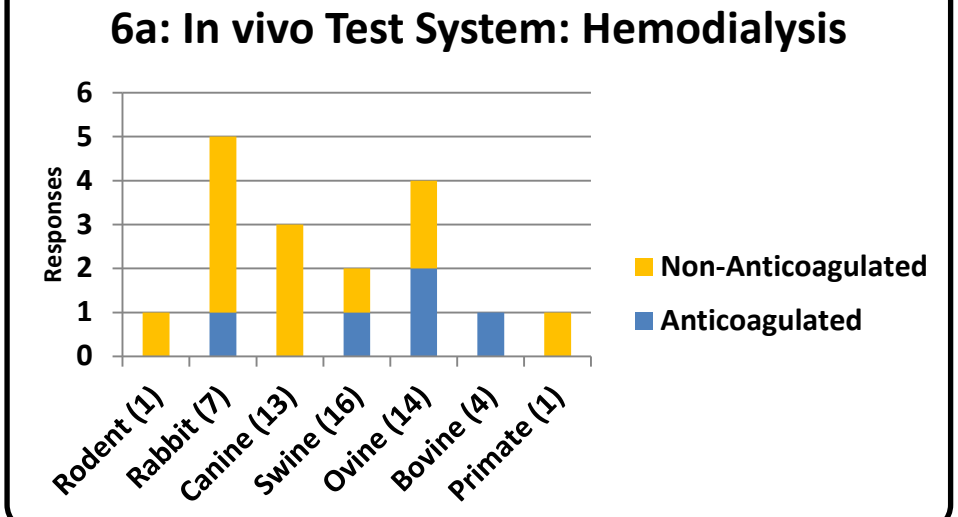
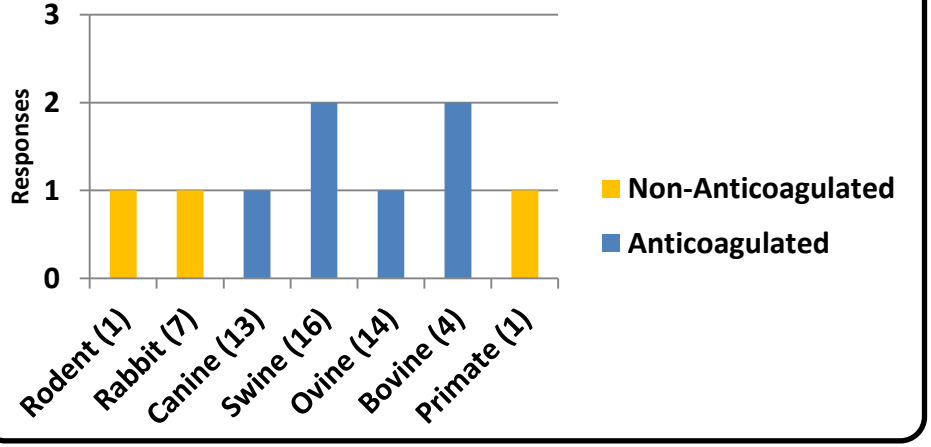
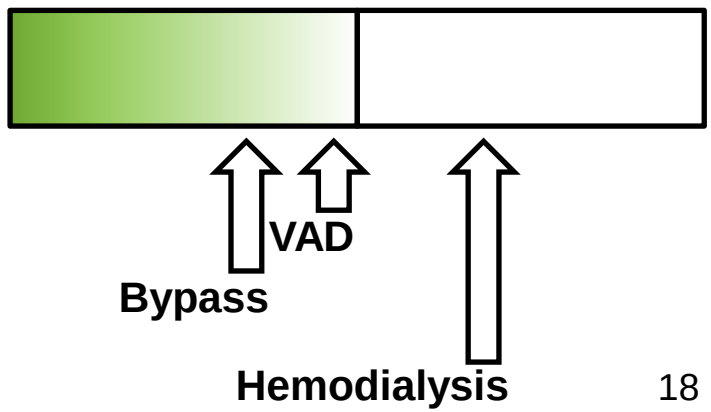
In vivo model system: device type









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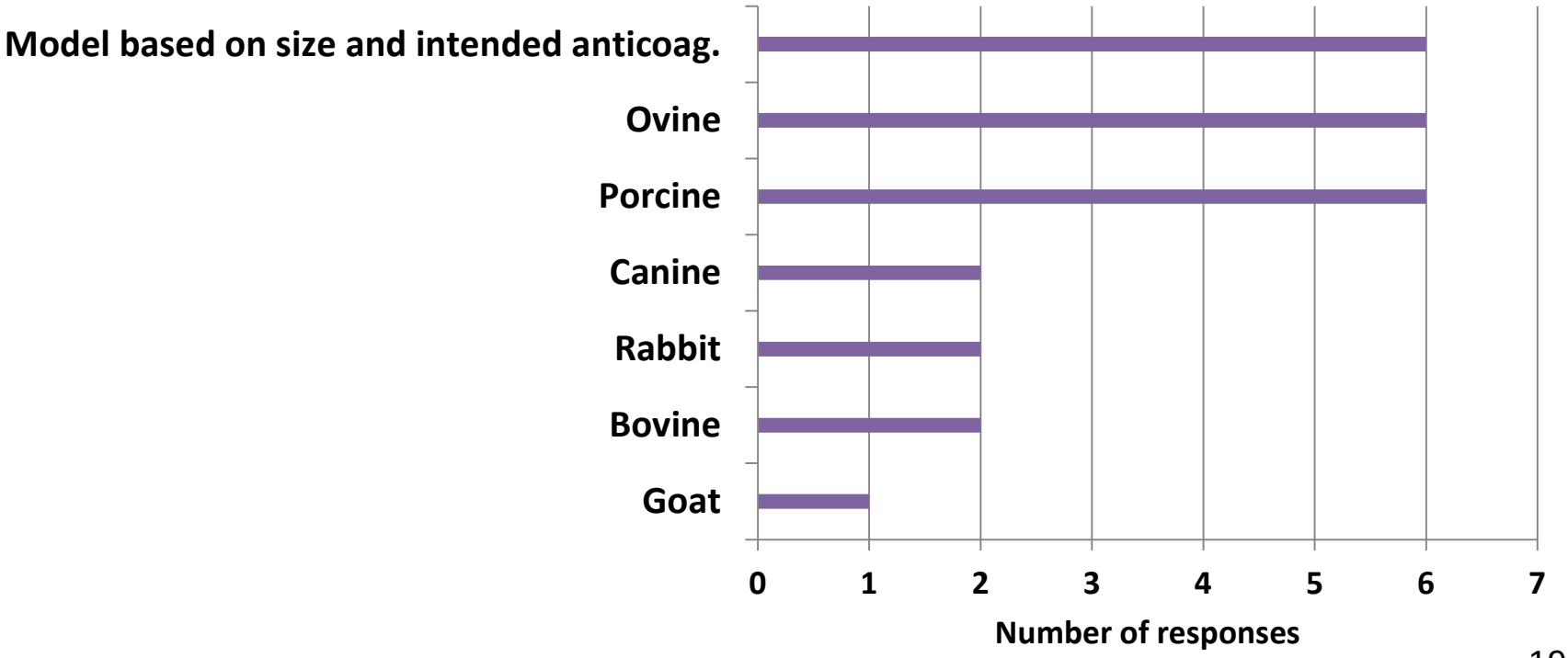
What is the most clinically relevant in vivo system to evaluate thrombogenicity?



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Conclusions

- Common in vivo endpoints included thrombus surface area, distribution, and weight; vessel patency; and gross pathology
  - Was not markedly different across devices
- Brand new device or material change most likely to result in thrombogenicity testing
  - Justification for omission of testing common for changes in device geometry
- Anticoagulation used in most device evaluation (exception of hemodialysis and catheters)
- Ovine and porcine were cited as most clinically relevant test species

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