What is “Normal” for CV Safety in Drug Development?

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Official Disclaimer

- The views presented in this presentation are the opinions of the presenter and not official policy statements of the FDA.

What is “normal” for CV safety in drug development?

What is normally:

- Done?
- Found?

What is normally done?
Four groups

1. Thorough QT (TQT) studies
2. CV safety studies for diabetic drugs
3. Drugs with a preclinical signal
4. Everything else

What is normally done? *Preclinical*

- *In vitro* receptor bindings/ion channels
  - Metabolites?
- Chronic toxicity studies
  - Rodents and nonrodents
  - Observations, lab, histopath
- CV safety pharmacology study
  - Usually in dogs
  - Hemodynamics, ECG

What is normally done?
Clinical

- Vital signs
  - Start and end of study
  - At trough drug levels
  - Sometimes at each visit
  - Quality of recording, e.g., BP?
- ECGs
  - Start and end at trough
  - No systematic reading of ECGs
- Adverse event (AE) reporting

What is normally done?
AE Reporting – CDISC SDTM

Identifiers

Variable Name	Variable Label	Type	Description
	Identifier Variables		
STUDYID	Study Identifier	Char	Unique identifier for a study.
DOMAIN	Domain Abbreviation	Char	Two-character abbreviation for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for variables to ensure uniqueness when datasets are merged.
USUBJID	Unique Subject Identifier	Char	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.
--SEQ	Sequence Number	Num	Sequence number given to ensure uniqueness of records within a dataset for a subject (or within a study, in the case of the Trial Summary domain).
--GRPID	Group ID	Char	Optional group identifier, used to link together a block of related records within a subject in a domain. --GRPID is also used to link together a block of related records in the Trial Summary dataset.
--REFID	Reference ID	Char	Optional internal or external identifier such as lab specimen ID, or UUID for an ECG waveform or a medical image.
--SPID	Sponsor ID	Char	Sponsor-defined reference number. Example: pre-printed line identifier on a Concomitant Medications page.

Events

Variable Name	Variable Label	Type	
	Topic Variable		
--TERM	Reported Term	Char	Topic variable name of the e
	Qualifier Variables		
--MODIFY	Modified Reported Term	Char	If the value fo text is placed
--DECOD	Dictionary-Derived Term	Char	Dictionary or --TERM, or t Equivalent to the Preferred Term (PT in MedDRA).
--CAT	Category	Char	Used to define a category of topic variables.
--SCAT	Subcategory	Char	Used to define a further categorization level for a group of --CAT values.
--PRESP	Pre-specified	Char	Used to indicate whether the event described by --TERM was pre-specified on a CRF. Value is 'Y' for pre-specified events, null for spontaneously reported events.
--OCCUR	Occurrence	Char	Used to record whether an event occurred when information about the occurrence of a specific event is solicited.
--STAT	Completion Status	Char	Used to indicate when a question about the occurrence of an event was not answered. Should be null or have a value of NOT DONE.
--REASND	Reason Not Done	Char	Reason not done. Used in conjunction with --STAT when its value is NOT DONE.
--BODSYS	Body System or Organ Class	Char	Body system or system organ class that a standard hierarchy such as MedDRA associated with an event.
--LOC	Location	Char	Describes anatomical location relevant for the event. Example: LEFT ARM for skin rash.
--SEV	Severity/Intensity	Char	The severity or intensity of the event. Examples: MILD, MODERATE, SEVERE.
--SER	Serious Event	Char	Is this is a serious event? Valid values are 'Y' and 'N'.
--ACN	Action Taken with Study Treatment	Char	Describes changes made to the study treatment as a result of the event. Examples: DOSE INCREASED, DOSE NOT CHANGED.
--ACNOTH	Other Action Taken	Char	Describes other actions taken as a result of the event that are unrelated to dose adjustments of study treatment.
--REL	Causality	Char	An opinion as to whether the event may have been due to the study treatment. Examples: NOT RELATED or POSSIBLY.
--RELNST	Relationship to Non-Study Treatment	Char	An opinion as to whether the event may have been due to a treatment other than study drug. Example: "More likely related to aspirin use."
--PATT	Pattern of Event	Char	Used to indicate the pattern of the event over time. Examples: INTERMITTENT, CONTINUOUS.
--OUT	Outcome of Event	Char	Description of the outcome of an event. Examples: RECOVERED/RESOLVED, FATAL.
--SCAN	Involves Cancer	Char	Was the event associated with the development of cancer? Valid values are 'Y' and 'N'.
--SCONG	Congenital Anomaly or Birth Defect	Char	Was the event associated with congenital anomaly or birth defect? Valid values are 'Y' and 'N'.
--SDISAB	Persist or Signif Disability/Incapacity	Char	Did the event result in persistent or significant disability/incapacity? Valid values are 'Y' and 'N'.
--SDTH	Results in Death	Char	Did the event result in death? Valid values are 'Y' and 'N'.
--SHOSP	Requires or Prolongs Hospitalization	Char	Did the event require or prolong hospitalization? Valid values are 'Y' and 'N'.
--SLIFE	Is Life Threatening	Char	Was the event life threatening? Valid values are 'Y' and 'N'.
--SOD	Occurred with Overdose	Char	Did the event occur with an overdose? Valid values are 'Y' and 'N'.
--SMIE	Other Medically Important Serious Event	Char	Do additional categories for seriousness apply? Valid values are 'Y' and 'N'.
--CONTRT	Concomitant or Additional Trtmnt Given	Char	Was another treatment given because of the occurrence of the event? Valid values are 'Y' and 'N'.
--TOXGR	Toxicity Grade	Num	Records toxicity grade using a standard toxicity scale (such as the NCI CTCAE). Sponsor should specify which scale and version is used in the Sponsor Comments column of the Define data definition document.

Timing

			Description
			umber. Numeric version of VISIT, used for sorting.
			scription of a clinical encounter.
			f VISIT. Should be an integer.
			the planned order of the Element within the Arm (see Section
			with the start date/time of the observation, or the date/time of collection if start date/time is not collected (see Section 3.2.2).
--DTC	Date/Time of Collection	Char	Collection date and time of an observation represented in ISO 8601 character format.
--STDTC	Start Date/Time of Observation	Char	Start date/time of an observation represented in ISO 8601 character format.
--ENDTC	End Date/Time of Observation	Char	End date/time of the observation represented in ISO 8601 character format.
--DY	Study Day of Visit/Collection/Exam	Num	Actual study day of visit/collection/exam measured in integer days. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC in Demographics. Should be an integer.
--STDY	Study Day of Start of Observation	Num	Start of observation expressed as study day relative to the sponsor-defined RFSTDTC. Should be an integer.
--ENDY	Study Day of End of Observation	Num	End of observation expressed as study day relative to the sponsor-defined RFSTDTC. Should be an integer.
--DUR	Duration	Char	Collected duration of an event, intervention, or finding represented in ISO 8601 character format.
--TPT	Planned Time Point Name	Char	Text description of time when a measurement or observation should be taken within a visit, as defined in the protocol. This may be represented as an elapsed time relative to a fixed reference point, such as time of last dose. See --TPTNUM and --TPTREF.
--TPTNUM	Planned Time Point Number	Num	Numeric version of planned time point used in sorting.
--ELTM	Planned Elapsed Time from Time Point Ref	Char	Planned Elapsed time in ISO 8601 character format relative to a planned fixed reference (--TPTREF) such as "Previous Dose" or "Previous Meal". This variable is useful where there are repetitive measures. Not a clock time or a date/time variable, but an interval, represented as an ISO 8601 duration.
--TPTREF	Time Point Reference	Char	Description of the fixed reference point referred to by --ELTM, --TPTNUM, and --TPT. Examples: Previous Dose, Previous Meal.
--RFTDTC	Date/Time of Reference Time Point	Char	Date/time for a fixed reference time point defined by --TPTREF in ISO 8601 character format.
--STRF	Start Relative to Reference Period	Char	Identifies the start of the observation as being before, during, or after the sponsor-defined reference period. The sponsor-defined reference period is a continuous period of time defined by a discrete starting point and a discrete ending point represented by RFSTDTC and RFENDTC in Demographics.
--ENRF	End Relative to Reference Period	Char	Identifies the end of the observation as being before, during or after the sponsor-defined reference period. The sponsor-defined reference period is a continuous period of time defined by a discrete starting point and a discrete ending point represented by RFSTDTC and RFENDTC in Demographics.
--EVLINT	Evaluation Interval	Char	Evaluation interval associated with an observation such as a finding --TESTCD represented in ISO 8601 character format. Example: -P2M to represent a period of the past 2 months as the evaluation interval for a question from a questionnaire such as SF-36.
--STRTPT	Start Relative to Reference Time Point	Char	Identifies the start of the observation as being before or after the sponsor-defined reference time point defined by variable --STTPT.
--ENRTPT	End Relative to Reference Time Point	Char	Identifies the end of the observation as being before or after the sponsor-defined reference time point defined by variable --ENTPT.
--STTPT	Start Reference Time Point	Char	Description or date/time in ISO 8601 character format of the sponsor-defined reference point referred to by --STRTPT. Examples: "2003-12-15" or "VISIT 1".
--ENTPT	End Reference Time Point	Char	Description or date/time in ISO 8601 character format of the sponsor-defined reference point referred to by --ENRTPT. Examples: "2003-12-15" or "VISIT 1".

What is normally analyzed?
AE Reporting

- Treatment emergent flag (or date)
- Discontinuation flag
- Serious flag/category
- Verbatim terms (original & final)
  - To derive coded “term” (MedDRA)

What is normally analyzed? *Verbatim terms*

- Original and final verbatim terms
  - Used for quality review
  - In a large study with 100,000+ AE reports, 21% changed
  - In a small study serious AEs obscured
  - CDISC SDTM does not support directly
- Inadequate verbatim terms
  - NDA words/AE: median 2, mean 2.1 (all), 2.6 (cardiac SOC)

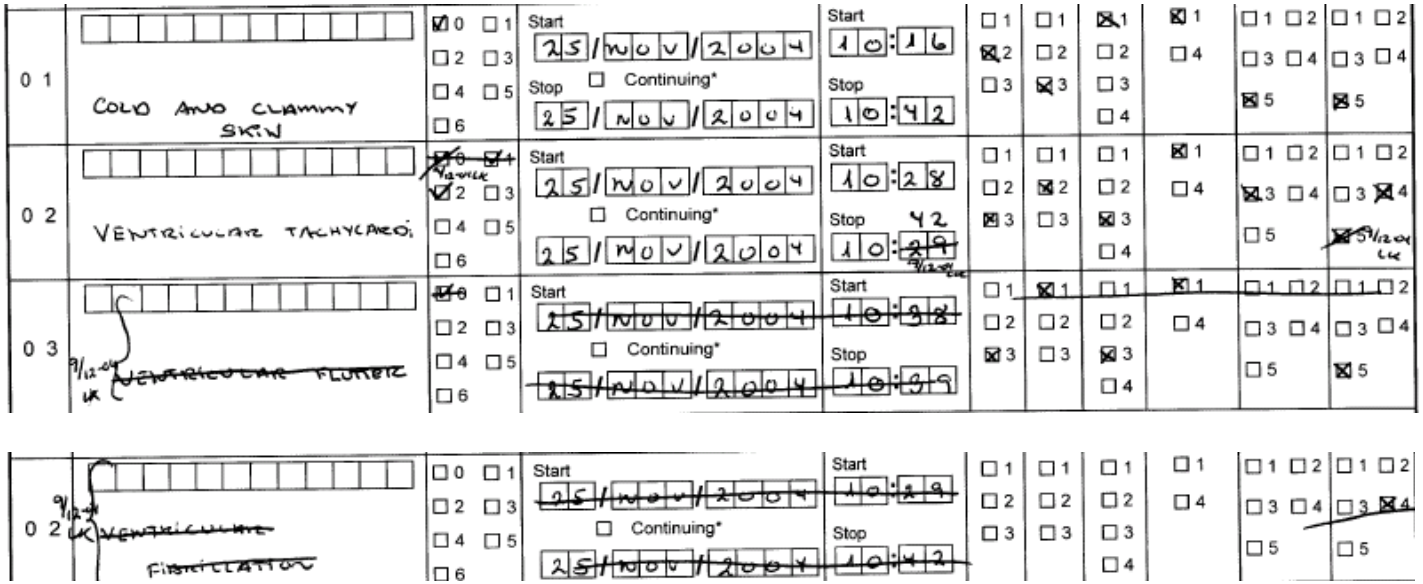
What is normally interpreted?
AE Reporting Supplements

- Case report forms per 21 CFR 314.50
  - Routine for deaths, discontinuations
  - Data queries not in SAS data sets
  - Serious AE forms (Medwatch reports)
- Narratives per ICH E3

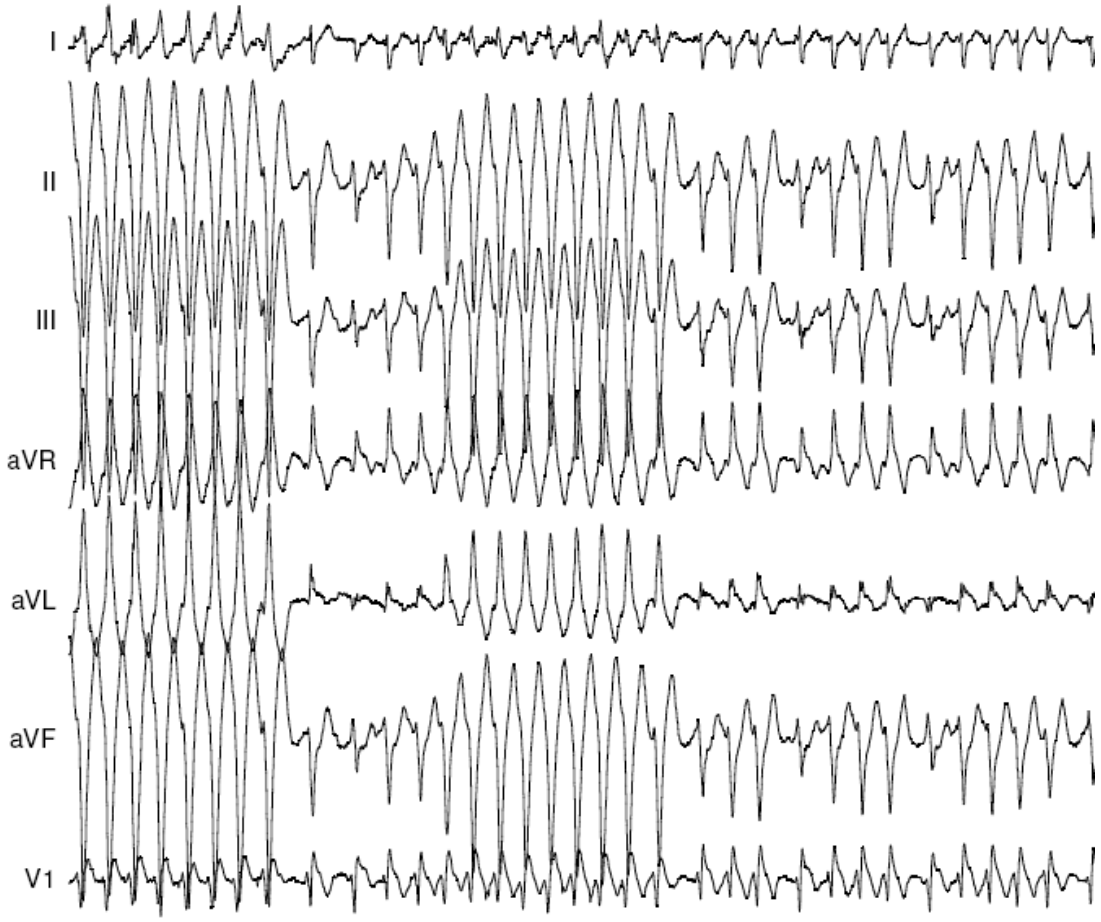
What is normally found?

- No simple answer
- Perhaps the better question:
  - What does the FDA find abnormal or suspicious?
- Real review examples
  - But some details may be left out to ~~protect the guilty~~ preserve confidentiality

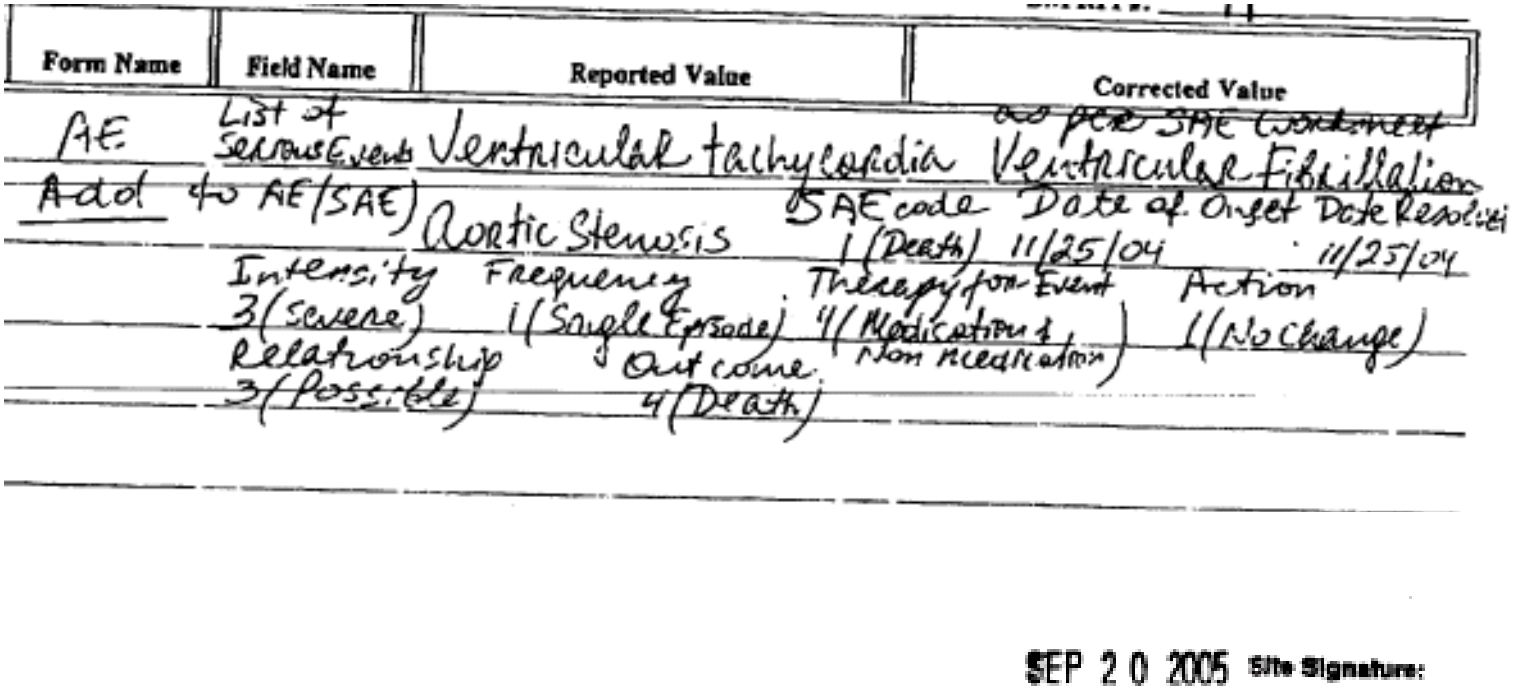
Example 1: How to avoid TdP in your development program



Tracing for the vtach – the initial rhythm upon deterioration



Data query for vtach



Form Name	Field Name	Reported Value	Corrected Value
AE	List of Serious Events	Ventricular tachycardia	Ventricular Fibrillation
Add to AE (SAE)		SAE code	Date of Onset / Date Resolved
	Aortic Stenosis	1 (Death)	11/25/04 / 11/25/04
	Intensity	Frequency	Therapy for Event / Action
	3 (Severe)	1 (Single Episode)	4 (Medication & Non medication) / 1 (No Change)
	Relationship	Outcome	
	3 (Possible)	4 (Death)	

SEP 20 2005 Site Signature:

Final AE terms

- Aortic stenosis
- Cold sweat
- Ventricular fibrillation

And no original verbatim AE terms were submitted!

Example 2: How coding can paint a rosy picture

By the sponsor's analyses, Drug A looks good:

	Primary MACE Endpoint		Secondary CV Endpoint	
	Drug A	Control	Drug A	Control
Primary Analyses				
Incidence (n)	20	18	46	42
Incidence (n/N)	0.009	0.011	0.020	0.026
RR (95%CI)	0.70 (0.38, 1.31)		0.69 (0.46, 1.03)	

What's not to like?

Errors of commission

- Sponsor's MACE: CV death, MI, stroke, ACS, revascularization
  - But 9 events in each group don't fit into these categories, e.g., angina but not unstable, TIAs
- Sponsor's secondary CV endpoint: plus arrhythmias, heart failure, "mechanical related events"
  - But includes trivial events, e.g., palpitations, sinus tachy & brady

Errors of omission

- Five drug and 1 control patient with events of “serious” and “severe” coronary artery disease are excluded from all of the sponsor’s CV safety endpoints
- What does a “coronary artery disease” event represent?

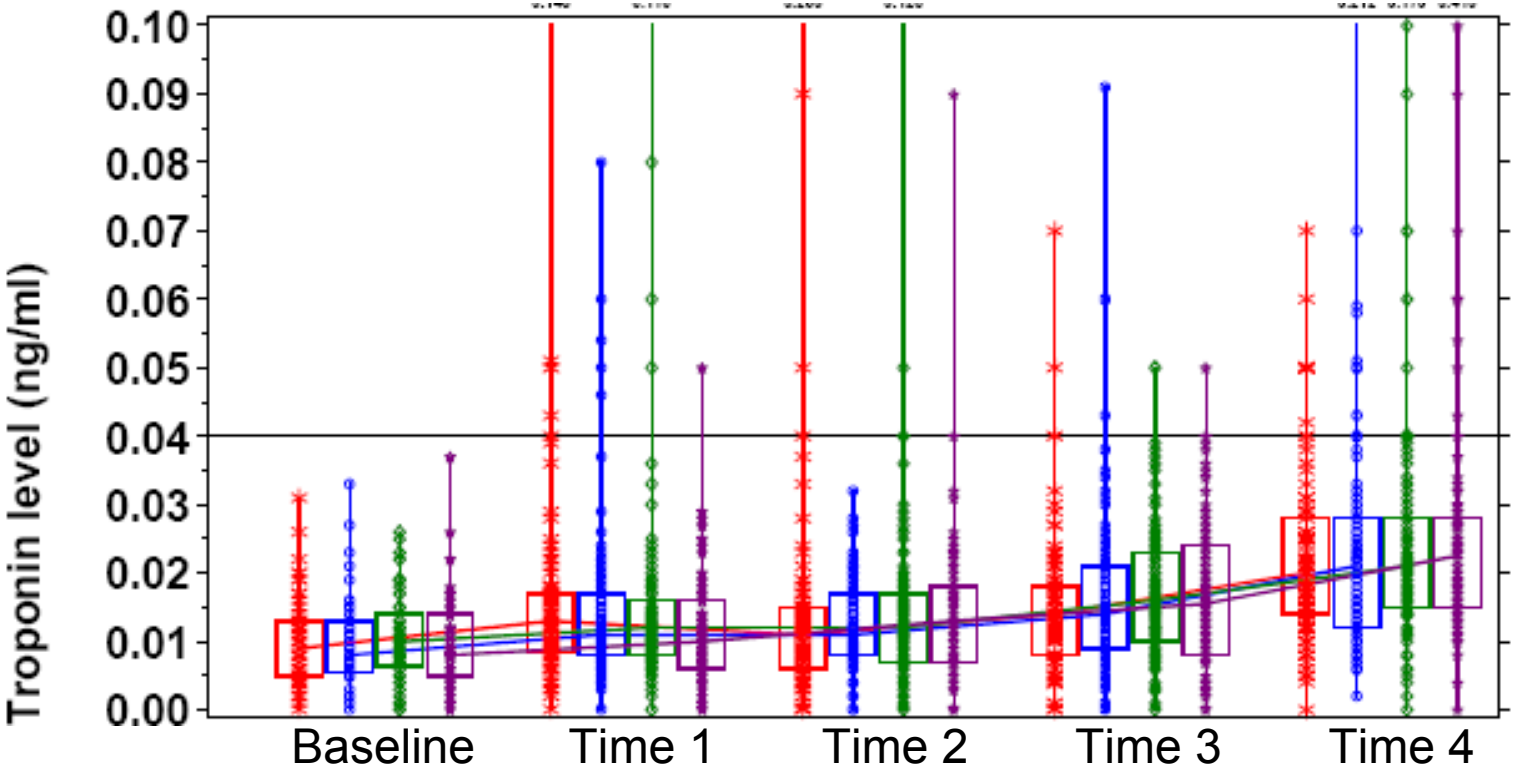
Not as rosy by usual coding

	CV death/MI/stroke		+angina/CAD/HF/TIA	
	Drug A	Control	Drug A	Control
Patients with events (n)	9	7	28	18
Percentage (n/N x 100)	0.4%	0.4%	1.2%	1.1%
Mantel-Haenszel RR*	0.84 (0.33 - 2.17)		0.98 (0.56-1.71)	

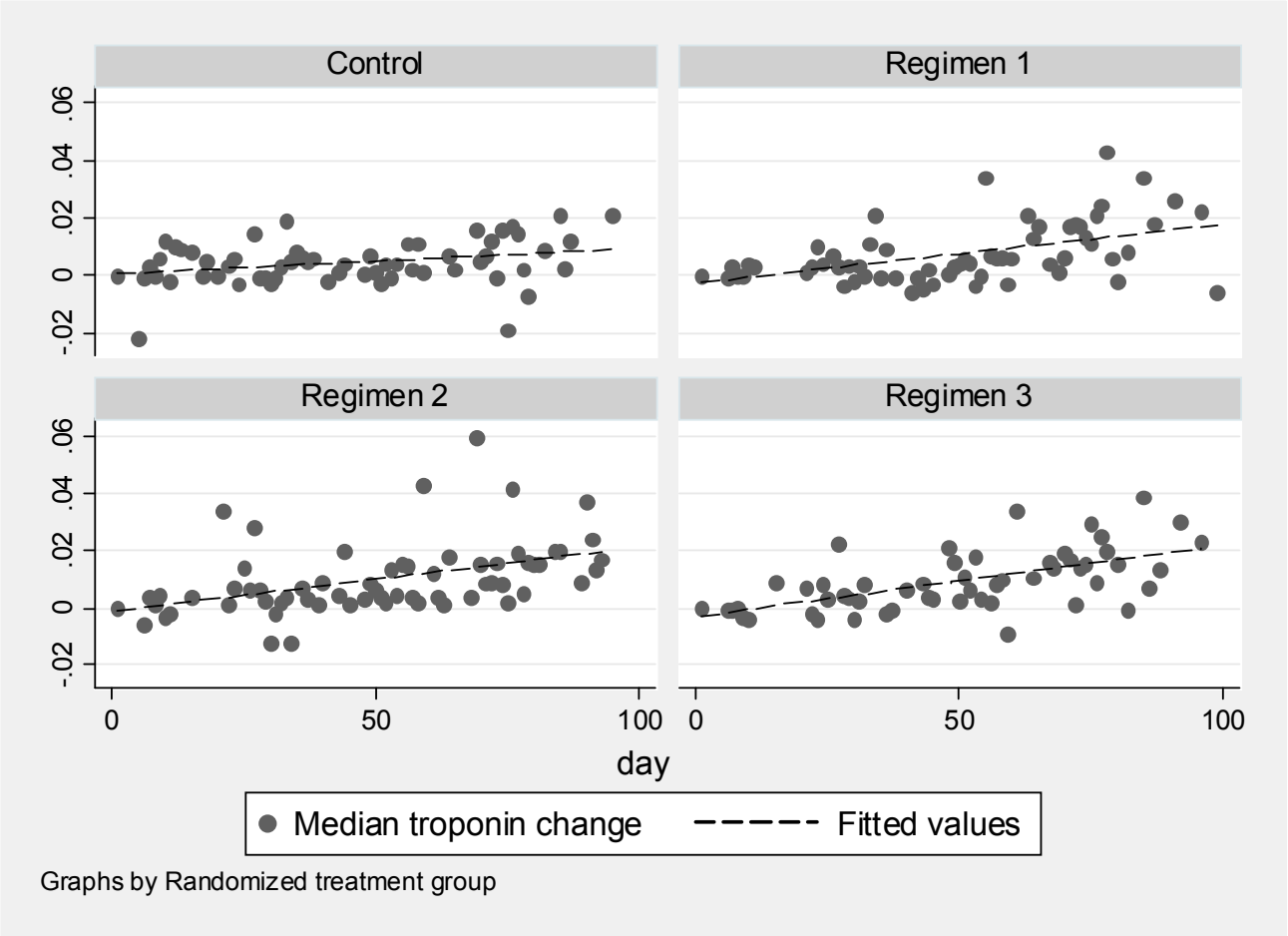
Example 3: Preclinical findings and insensitive analyses

- Drug A shows evidence of cardiac toxicity in a dog study
  - Myocardial hypertrophy & necrosis
  - Preceded by troponin elevation
- Follow-up study in another species
  - Sensitive troponin assay
  - Erratic sampling not at peak drug levels
  - Concomitant use of another agent known to cause troponin increases & cardiomyopathy

Sponsor's analysis of follow-up study of troponin increases



FDA analysis of follow-up study of troponin increases



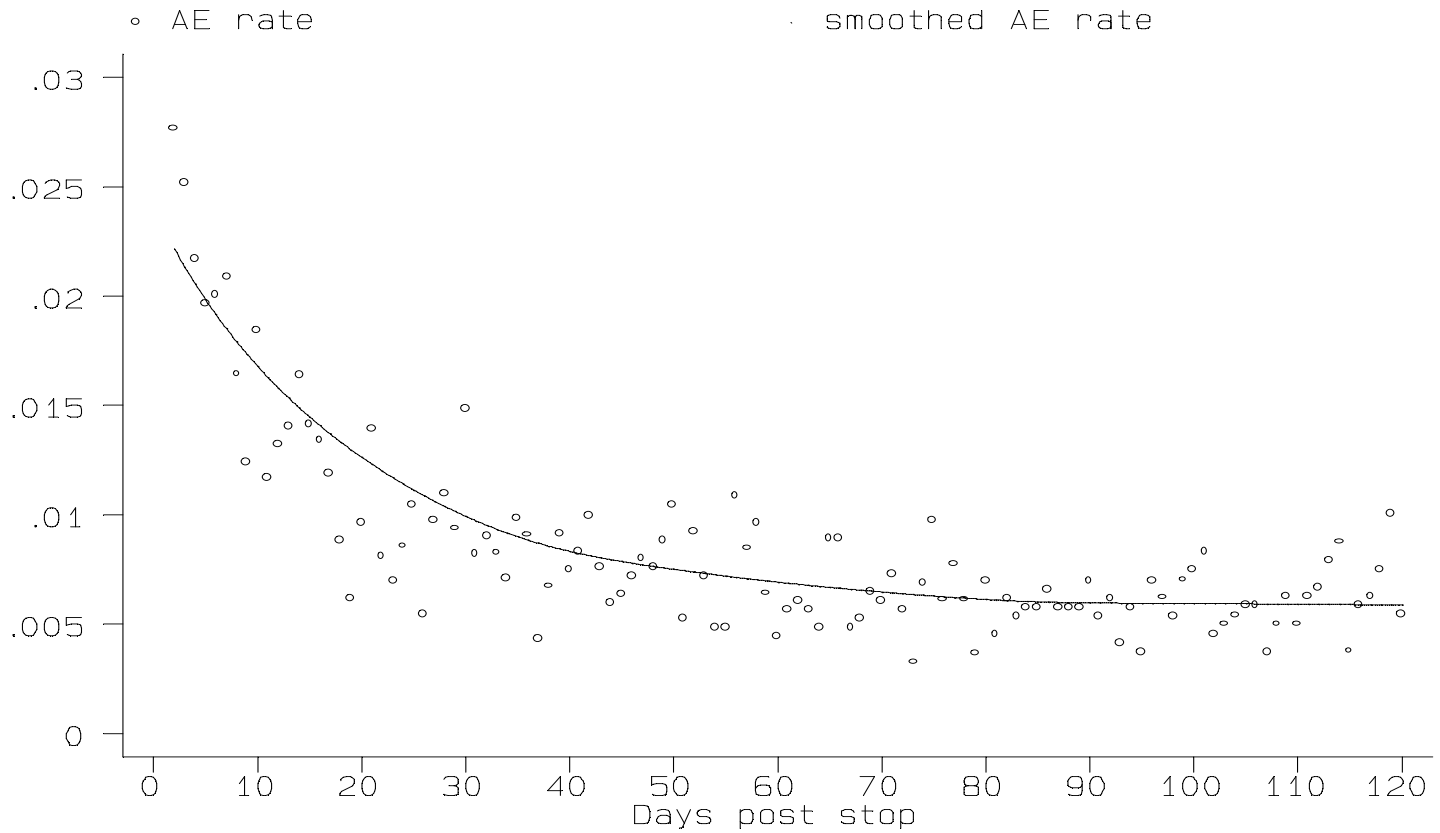
Example 4: Putting it all together in real LIFE

- The LIFE Study
  - losartan vs. atenolol
  - 9,183 patients with hypertension & LVH
  - 4.8 years mean f/u
- Primary EP – CV death/MI/stroke
  - 13% risk reduction, p = 0.021
  - Virtually all stroke: 25% risk reduction

LIFE: What were the stroke types?

- Predominantly ischemic non-embolic
  - 73% losartan vs. 75% atenolol
  - But CRF review revealed several “non-embolic” strokes in young individuals with atrial fibrillation (afib) not on warfarin!
- Afib by sponsor’s analyses not different
  - 2.1% losartan vs. 2.0% atenolol SAEs
  - But sponsor used a 14-day cutoff post drug d/c for AEs

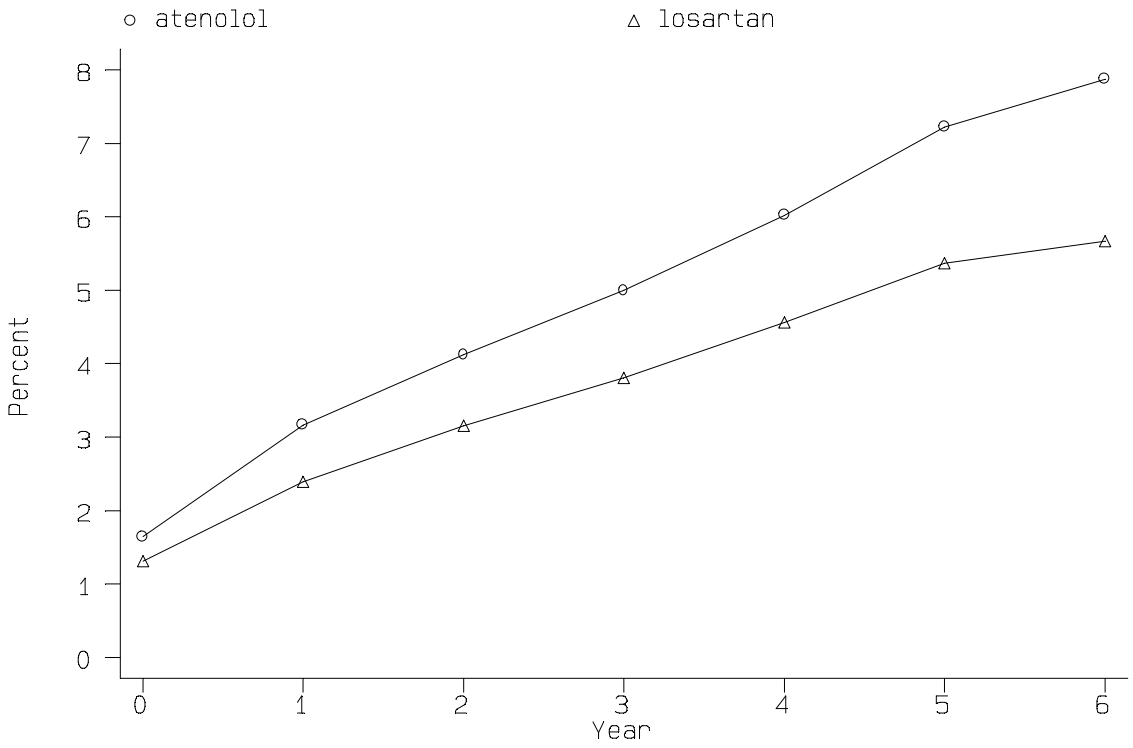
AE rates after drug D/C in LIFE



Afib AE rates in LIFE

	atenolol	losartan
Any afib AE	7.9%	6.8%
Afib AE leading to withdrawal	1%	0.5%

Cumulative rates of afib on annual ECGs in LIFE



Lessons from LIFE

- The mechanism may not be what you project
  - 50% of the stroke difference due to afib
  - 25% due to a silly mm BP difference
- CRF review can be revealing
- AE rates need careful, informed calculation
- AE findings are usually subtle
- It's nice to have confirmation!