Population Differences Case Examples: Lessons from Past Trials

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Clin Pharm (PK and PD) Usually Explains Differences, but

- Not always
- You may not have looked at the right PD
- How much PK difference makes a clinical difference?

So, it is always good to look for subset differences (but don't always believe them).

I will show a number of cases, divided as

- Pure PK – blood level alone tells you.
- PK/PD - might not have appreciated the impact of small PK differences (steep C/R relationship).
- PD (genetics, pathophysiology).
- Unpredictable – illustrates why you should always look.

Pure PK

We routinely adjust doses for alterations in renal function (reducing dose in people with reduced function, but see NOACs later) and for drug-drug interactions (2D6 inhibitors increase tricyclic blood levels by 8-fold).

We generally ignore small blood level differences (but that is because most D/R and C/R relationships are relatively flat in the therapeutic range).

For toxic drugs (or maybe more broadly for drugs we know have steep D/R curves for effect and/or toxicity (cytotoxic oncology drugs) we often dose by weight.

PK/PD

It is not always easy to know what effect small PK differences will have, e.g., we don't usually adjust dose for smaller size (gender), age-related falls in renal function, but in some cases small differences do matter.

- We know a variety of factors (genetic, food, drugs) affect warfarin blood levels, and we do worry about small changes; fortunately we have a good and easy way to measure the anti-coagulant effect, INR, so we monitor that.

- For hypnotics, we know size and renal function can affect blood levels (elderly tend to get higher levels and have often had lower recommended doses) although for Halcyon there was also a PD difference – the SAME blood levels caused more dizziness, etc. in older patients.

PK/PD (cont)

For zolpidem, although we knew the same 10 mg dose would give higher average blood levels in women (smaller), there were no apparent differences in S or E, but a more sensitive PD marker led to lowering the dose.

We found that women were more likely than men to have morning blood levels high enough to impair driving performance, a realization made possible by a study that linked impairment on a driving test to blood levels over a certain threshold.

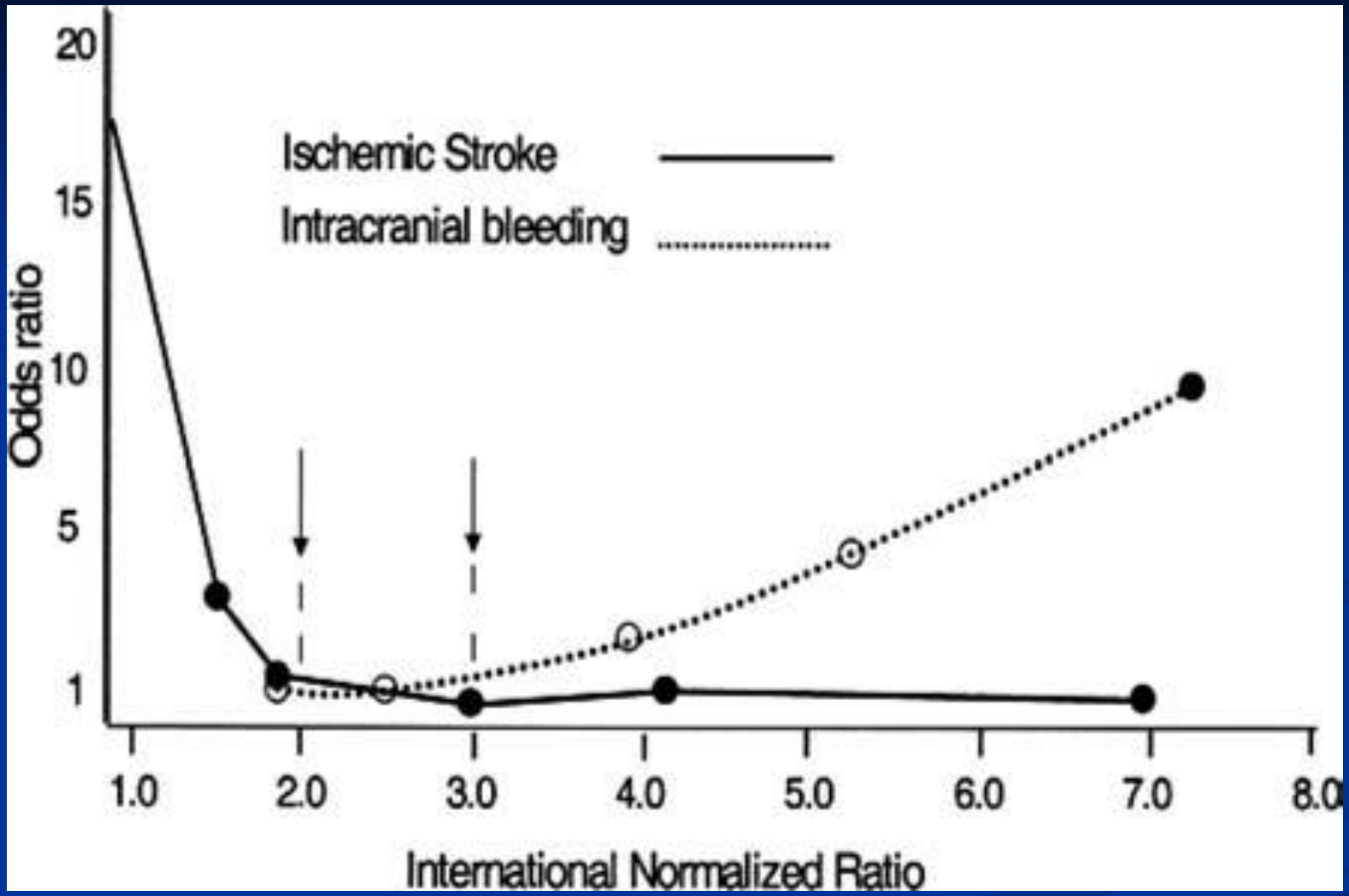
So, getting the right and very sensitive PD marker was crucial to realizing that the dose needed to be reduced in women.

- Amlodipine had far more cases of fluid retention in women given the 10 mg dose, presumably reflecting greater blood levels.

PK/PD (cont)

- For the NOACs, or at least dabigatran and edoxaban, we have extremely good data relating trough blood levels to the two critical endpoints when NOACs are used to treat AF
  - thromboembolic stroke
  - serious bleeding

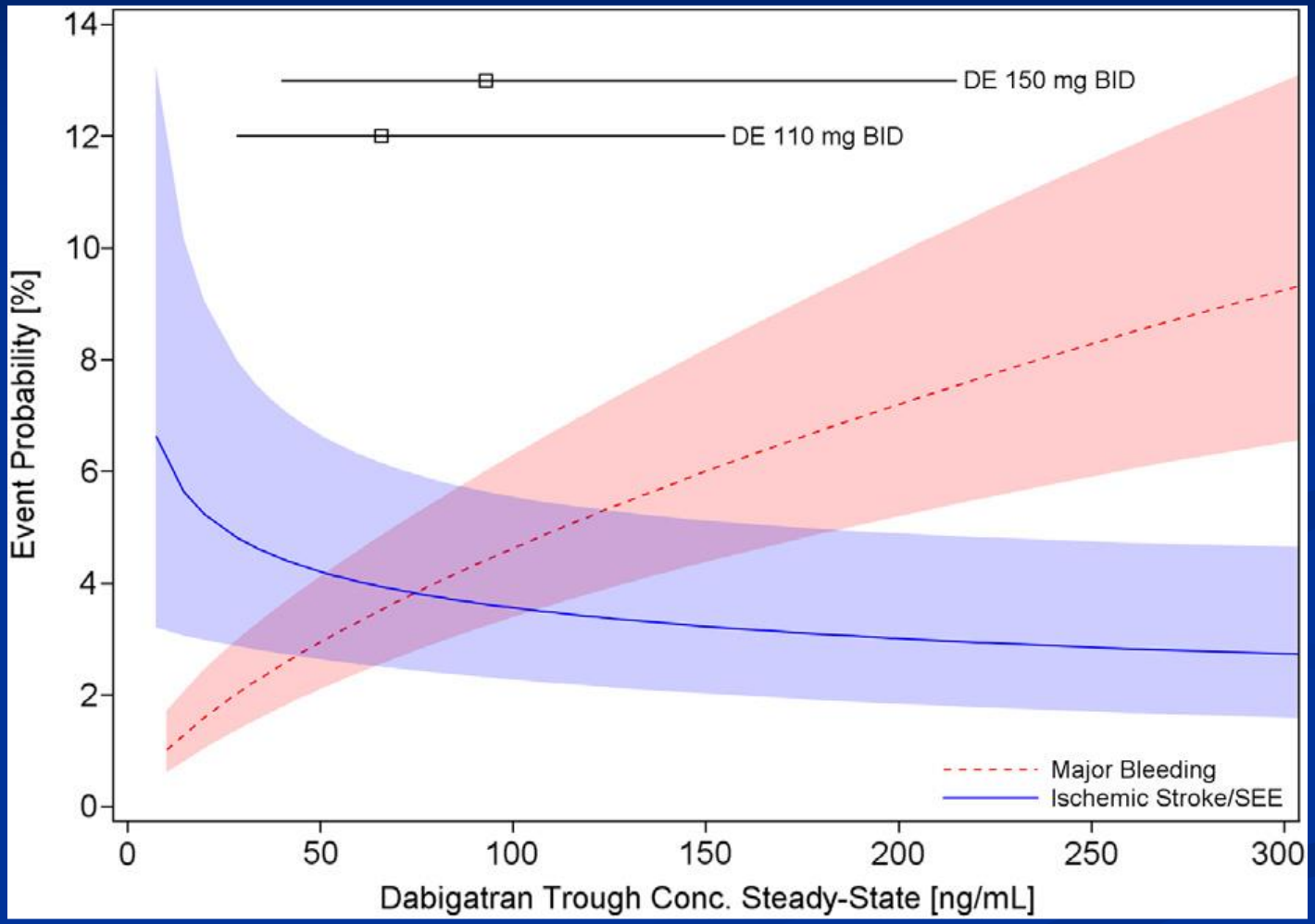
We knew that blood levels (translated into INR) corresponded to stroke rates and both intracranial and overall bleeding for warfarin. There is a "sweet spot" of INR 2-3 that optimizes stroke effect without too much bleeding. So the highly variable PK is really managed by assessing a relevant PD effect.


Ischemic Stroke
Intracranial bleeding
Odds ratio
20
15
10
5
1
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
International Normalized Ratio

PK/PD (cont)

NOACs (cont)

For dabigatran we saw, as for warfarin, that there was a threshold level for optimal stroke effect, about 75-150 ng/ml, with relatively little bleeding. This was clear from the clinical trial RE-LY, where the small difference between 150 mg and 110 mg had a marked effect (28% reduction) on stroke rate because it put almost everyone into the right concentration range. On the other hand, some people on 150 mg have blood levels greater than needed for optimal stroke reduction, at a cost of bleeding. And there is not yet any equivalent of an INR. It seems possible that measuring trough dabigatran levels could allow appropriate adjustment.


14
12
10
8
6
4
2
0
Event Probability [%]
DE 150 mg BID
DE 110 mg BID
Major Bleeding
Ischemic Stroke/SEE
0
50
100
150
200
250
300
Dabigatran Trough Conc. Steady-State [ng/mL]

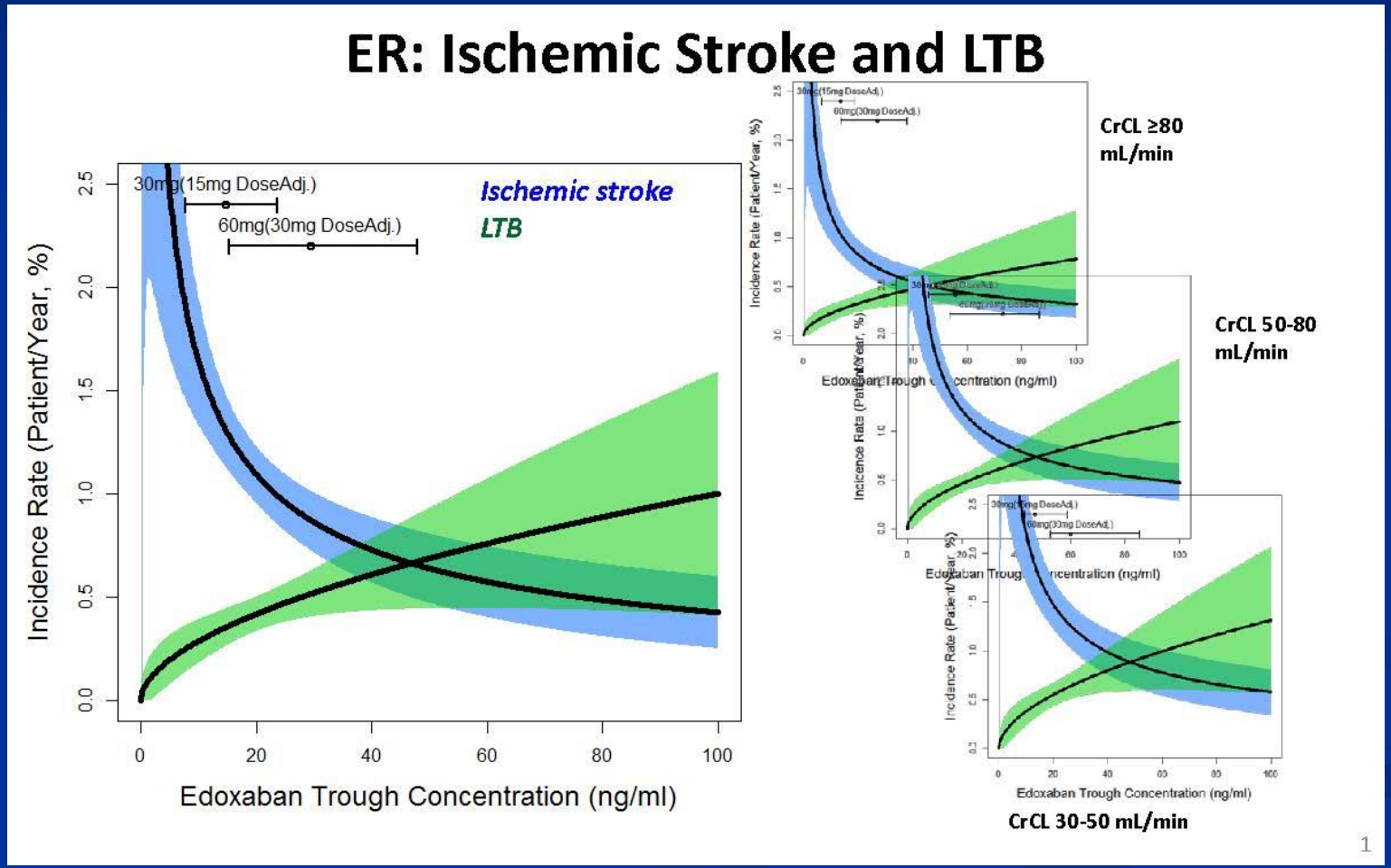
PK/PD (cont)

NOAC's (cont)

The most recent NOAC, edoxaban, revealed substantial differences in effect with dose but, in addition, based on renal function, with stroke rates greater than warfarin if CrCl was > 95 ml/min. The drug was not approved for the patients with CrCl > 95 ml/min. Moreover, the best results on ischemic stroke were in patients with mild renal impairment (CrCl 50-80). The controlled trial thus showed a striking relationship between renal function and outcome.

This is still clearer in the relationship of trough levels to stroke rate (PK/PD), which is similar in people over the full range of renal function.

PK/PD (cont)



Source: NOAC Presentation by Jeffry Florian

PK/PD (cont)

NOACs (cont)

One's first thought is that even a simple blood level of edoxaban could lead to a substantial outcome improvement, although we recognize that desirability of not having to monitor anticoagulants and the NOACs at single doses (same reduced for low renal function) do as well as warfarin, with less hemorrhagic stroke. A single drug blood level measurement might nonetheless be acceptable. A more intriguing possibility, however, is that adjustment of dose renal function might get almost everyone into the right range.

We are actively pursuing this possibility and it seems likely we can place a very large fraction of people into the "sweet spot" by adjusting dose for renal function.

Pharmacodynamic

- Growing fast, genetic factors that determine response of a tumor, of a hepatitis C strain, or of a subset of cystic fibrosis patients.

  You will hear about all these. Similar in some ways to antibiotic sensitivity.

- Classic case was high and low renin hypertension, with former responding very well to ACEIs, ARBs, and BBs, the latter responding minimally. In this case we understood the reasons for the difference.

PD, But Not Fully Understood

The first rule of everything is

You're almost never quite smart enough

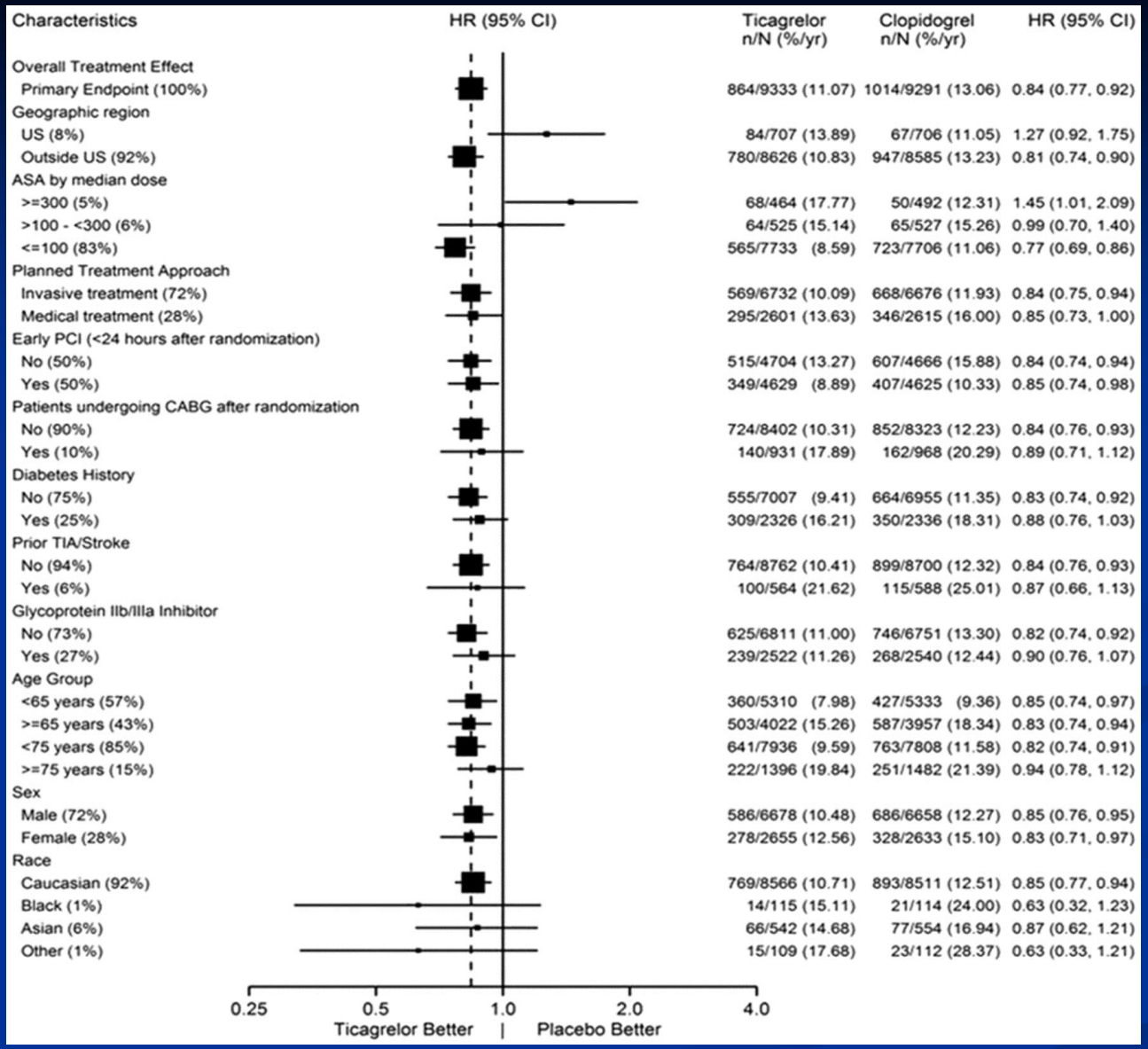
There are therefore cases of population differences where the differences surprise us. They are presumably PD-related, but not for reasons we know (at least not yet). A few illustrations:

- Angioedema appears to be more common in blacks than whites but the increase in risk of angioedema from ACEIs is also greater in blacks. Reichman, et al recently reported this for the Medicare population.
- Alosetron, a drug for diarrhea – predominant IBS appeared to be effective only in women and was approved only for women.

PD, But Not Fully Understood

- Ticagrelor

In the PLATO study of ticagrelor, early analyses showed an effect on CV mortality and non-fatal MI, in all regions but the US. This was shown to result from the use of higher aspirin doses in the US in about 50% of patients vs 7% elsewhere and ticagrelor's effect was reduced in people receiving higher dose aspirin. Corrected for ASA dose, results were similar in the US and elsewhere. The reason for the aspirin effect is not known, but the case illustrates how important it can be to examine subsets for possible differences.



Source: Alison Blaus et al. Circulation. 2015;132:1425-1432

PD, But Not Fully Understood

- BiDil

  Two early VA studies in CHF strongly suggested that there was a response (a strong one) to BiDil only in self-identified blacks.

There actually was reasonably persuasive evidence that the effect of BiDil in whites was small, at best. There were <u>two</u> previous studies, V-HeFT 1 and 2, that pretty convincingly showed, at best, a much smaller effect in whites.

BiDil

VHeFT 1

	Overall (459)		Blacks (128)		Whites (324)	
	BiDil	Plbo	BiDil	Plbo	BiDil	Plbo
Annualized mortality			9.7%	17.3%	16.9%	18.8%
RR	0.73		0.34		0.75	
P	0.09		0.004		0.11	

VHeFT 2

	Overall (804)		Blacks (215)		Whites (574)	
	BiDil	Enal	BiDil	Enal	BiDil	Enal
Annualized mortality			12.9%	12.8%	14.9%	11.0%
RR	1.23		0.95		1.48	
P	0.08		0.83		0.009	

PD, But Not Fully Understood

We therefore allowed a trial in ONLY self-identified blacks, with quite spectacular results.

	BiDil N=518	Placebo N=532	Risk Reduction
All Cause Mortality	6.2%	10.2%	43% (p=0.012)
First CHF Hosp'n	16.4%	24.4%	39% (p=0.001)

As noted, we don't know why BiDil is more effective in blacks, but it clearly seems to be the case.

Conclusion

There are enough cases of subset differences to suggest that it is always worth looking at subsets.

But, of course, be careful in reading conclusions (impact of zodiacal signs in ISIS I).

It is now SOP to do forest plots of any outcome study and they are often included in labeling. Our regulations call for analyses of effectiveness and safety results by age, sex, race, and other characteristics of interest.