Balance on CV Safety
Do We Have It Right?

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CV Safety and State of the Art Development Issues
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Issues

There are two distinct issues in evaluating CV safety”

1. What data to have
2. How to balance B and R, which includes assessment of ability to influence behavior.

Need for Data

We have always known that drugs have risks. Historically we have focused on rare serious adverse effects (SJS, agranulocytosis, TdP, liver necrosis) whose risk was greatly increased by drugs, but there is new interest in much smaller increases in relatively common events, especially CV events, of the kind clearly shown for

- Anti-arrhythmics (CAST, quinitine)
- CHF drugs (milrinone, flosequinan, vesucerinone)
- Erythropoietin
- Torcetrapib

  and suspected for
- Oral hypoglycemics
- NSAIDs

[I have extra slide showing reasons for drug withdrawal over time that illustrates this change.]

Need for Data

Many of these adverse outcomes emerged from studies attempting to show CV benefit (CAST, torcetrapib, erythropoietin) or other benefits (NSAIDs, less bleeding or effects on polyps; diabetic complications, UGDP, ACCORD) but some reflected an ongoing concern about possible harm (inotropes for CHF, anti-arrhythmics generally) and were seeking reassurance.

An interesting question is whether showing an advantage over other treatment implies the inferior treatment is harmful, as the following results could suggest.

Need for Data

a. LIFE study: losartan gave less stroke than atenolol. Implications?

b. The ACCOMPLISH (NEJM, 2008) trial compared amlodipine (5-10 mg) and HCTZ (12.5-25 mg), each added to benazepril. Amlodipine had fewer events (MACE & CV hospitalizations), 11.8% vs 9.6%, a 20% risk reduction for MACE alone, HR was 0.79 (p=0.002). BP control was very similar in both groups.

c. Dabigatran (RE-LY); RE-LY showed significant reductions in both ischemic and hemorrhagic stroke for dabigatran 150mg vs Coumadin.

Need for Data

For many years (since the 1980's) Cardio-Renal has insisted on reassuring outcome studies for all drugs intended for chronic CHF and, since CAST, for all anti-arrhythmics. Many CHF drugs, either direct sympathomimetic inotropes or phosphodiesterase inhibitors, proved lethal and were never approved. Other drugs (ACEI's, beta blockers, and spironolactone) had favorable CV outcomes. No drug intended for long-term symptomatic benefit alone (i.e., without an outcome claim) has been submitted but it seems probable we would want at least reassuring outcome data.

Need for Data

Post-CAST we have sought assurance, in at least some setting, of lack of harm.

DL sotalol for preventing AF recurrence had the post-AMI Julien trial (NS, but 18% reduction of mortality) while dofetilide had 2 "Diamond" studies showing no adverse outcome in CHF and post-infarction. Dronedarone showed increased mortality in patients with recent CHF exacerbation but the large effectiveness trial supporting approval (ATHENA), which excluded such patients, showed a favorable survival trend and a highly significant reduction in cardiovascular hospitalizations.

Need for Data

Brass, Lewis, Lipicky, Murphy, and Hiatt proposed some years ago in CP and T that for symptomatic CV treatments (where outcome is not part of development as it would be for, say, antiplatelet therapy) sufficient data should be obtained to rule out some upper boundary of risk, perhaps 50% (HR < 1.5). This conclusion would presumably also apply to approvals based on a surrogate endpoint, and seems potentially applicable to a wide range of chronically used drugs.

Brass, et al, recognized many difficulties.

- Long-term placebo-controlled trials in symptomatic patients will not be possible, leaving only comparative trials available; even in outcome trials, placebo controls will often not be possible.
- Trials of realistic size require high risk people to gain enough endpoints and will almost surely require a combined endpoint (death, AMI, stroke and perhaps more, like unstable angina, CHF, etc) but that may not be what one is worried about (CHF drugs, CAST, do not show increased AMI or stroke). So the size must be still greater if there is only one endpoint of interest or if the population is healthier.

Need for Data

We have not sought such outcome data for antihypertensives. It would be difficult, as ALLHAT showed, because all patients get multiple drugs. Moreover, through dozens of studies we have been reassured that all drugs seem to be beneficial (although, as noted, perhaps not all the same). ALLHAT was also reasonably reassuring on this point.

We have also not sought such data pre-approval for LDL-lowering drugs, although outcome studies are invariably done post-approval.

As everyone knows, we have produced guidance calling for outcome data pre and post-approval for diabetes treatments and are actively discussing the issue for weight loss drugs, probably because of their difficult history (in contrast, say, to anti-hypertensives).

Need for Data

We are clearly going case by case and conclusions appear to reflect.

- The populations treated, both because risk status is critical with respect to potential harm, and because the trials need high risk people to be useful.
- The likelihood of long-term use.
- Past history (antiHT and statins have been beneficial; weight loss drugs have been troublesome; oral hypoglycemics have unclear effects on cardiovascular outcomes.

There is always concern the increased expectations will cut off development, although it is noteworthy that 10-25,000 patient trials of anti-platelet drugs and anti-coagulants are everywhere.

Need for Data

It should be noted that the modest increases in CV risk seen with various drugs can almost certainly not be detected except with larger RCTs.

Need for Data
Value, Cost-Benefit

- Requiring outcome data, not surprisingly, can affect development. Antiarrhythmic policy is "associated with" with minimal anti-arrhythmic development (implanted defibrillators may have influenced also) and CHF treatments other than ACEIs, ARB's, eplerenone are hard to spot.

- How likely, absent an animal or human signal, is a bad outcome? If these are very hard to detect, and detection is uncertain, how worthwhile is it compared to other important questions (how low to drive BP, LDL cholesterol) that also have life and death implications?
- There is no doubt that expanded ability to conduct large trials (e.g. in HMO-type environments) would greatly enhance our ability to do such trials.

Balancing B/R

Sometimes a serious risk is recognized and is potentially avoidable, if patients and physicians pay attention. There are several situations.

1. Drug has unique benefit/advantage

In general when this is the case we will approve it with conditions of use to mitigate the risk, the conditions ranging from advice to limited distribution.

Advice

- Dronedarone – no recent CHF
- Bosentan – pregnancy testing, limited distribution
- Wide range of contraindications, D & A instructions, Warnings/Precautions

Balancing B/R

2. Drug has a major risk alternatives do not have and no unique population

Generally drug is WD; no good reason to use

- Bextra
- Troglitazone
- Bromfenac, suprofen, benoxaprofen
- Terfenadine, astemizole
- Mibefradil
- Cerivastatin
- Rofecoxib
- Pemoline

But may wait till alternative

- Fexofenidine without TdP
- Rosi/Pioglitazone without hepatotoxicity

Conclusions

There is little doubt that there is a new interest in conducting studies to detect possible modest adverse (or beneficial, of course) effects of chronic-use drugs. Interest has spread from cardiovascular drugs (where it has long been present because of experience with anti-arrhythmics, various inotropes) to other chronic-use drugs, including anti-diabetics, NSAIDs, and weight-loss drugs. Of course, some drugs have their effectiveness evaluated in long-term studies (anti-platelet drugs, bisphosphonates and other bone-preserving agents, adjuvant chemotherapy) that are of substantial size. These studies can already detect an adverse long-term effect, at least if the right population is studied.

There is no doubt that this issue will be the subject of much discussion. So far, however, I think we have it about right.

Table 1: History of Drug Safety Withdrawals

Drug	Year Approved	Year Withdrawn	Data Source	Adverse Effect
azaribine (Triazure)	1975	1976	1	Arterial thrombosis
phenformin		1978	2	Lactic acidosis
ticrynafen (Selacryn)	1979	1980	1	DILI
benoxaprofen (Oraflex)	1982	1982	1	DILI
zomepirac (Zomax)	1980	1983	1	Anaphylaxis
methaqualone (Qualude)	1960's	1984	1	Overdose very hard to treat
nomifensine (Merital)	1984	1986	1	Hemolytic anemia
suprofen (Suprol)	1985	1987	1	Acute renal failure
*encainide (Enkaid)	1986	1991	3a	Mortality (HR=2)
temafloxacin (Omniflox)	1992	1992	1	Hemolysis, renal failure
flosequinan (Manoplax)	1992	1993	3a	Mortality (HR – 1.5)
fenfluramine (Pondimin)	1973	1997	2	Valvulopathy
terfenadine (Seldane)	1985	1998	1, 4	TdP
mibefradil (Posicor)	1997	1998	1	Drug-drug Interactions causing TdP and rhabdomyolysis
bromfenac (Duract)	1997	1998	1	DILI
** trovafloxacin (Trovan)	1997	1998	1	DILI
astemizole (Hismanil)	1988	1999	1, 4	TdP
grepafloxacin (Raxar)	1997	1999	1, 4	TdP
troglitazone (Rezulin)	1997	2000	1	DILI
cisapride (Propulsid)	1993	2000	1, 4	TdP
*** alosetron (Lotronex)	2000	2000	1	Ischemic colitis; constipation needing surgery
PPA (phenylpropanolamine)	<1962	2000	2	Hemorrhagic stroke
rapacuronium (Raplon)	1999	2001	1	Bronchospasm
cerivastatin (Baycol)	1997	2001	1, 2	Higher rate of rhabdomyolysis than other statins
Etretinate	1986	2002	1	Birth defects
Levacetyl methadol (0rlaam)	1993	2003	1, 4	TdP
rofecoxib (VIOXX)	1999	2004	3a	AMI
*** natalizumab (Tysabri)	2000	2005	1	PML
pemoline (Cylert)	1975	2005	1	DILI
valdecoxib (Bextra)	2001	2005	1	Stevens-Johnson Syndrome
gatifloxacin (Tequin)	1999	2006	1	Hyperglycemia and hypoglycemia
pergolide (Permax)	1998	2007	2	Valvulopathy
tegaserod (Zelnorm)	2002	2007	3b	CV events
aprotinin (Trasylol)	1993	2008	3a	Increased mortality
sibutramine (Meridia)	1997	2010	3a	CV events
propoxyphene	2010		2, 4	Mortality, esp in overdose

Data Sources:
1= individual cases
2 = epidemiologic data
3 = RCT's: 3a large trials; 3b MetaA
4 = Evidence of QT prolongation
* Important toxicity, but withdrawal not FDA encouraged
** NOT withdrawn, but limited
*** Returned to market

DILI = drug induced liver injury
TdP = torsade de pointes
PML = progressive multifocal leukoencephalopathy

Table 1 shows drugs withdrawn for safety reasons since 1970.