How Modified PEM supports Risk Management: a selected brief overview

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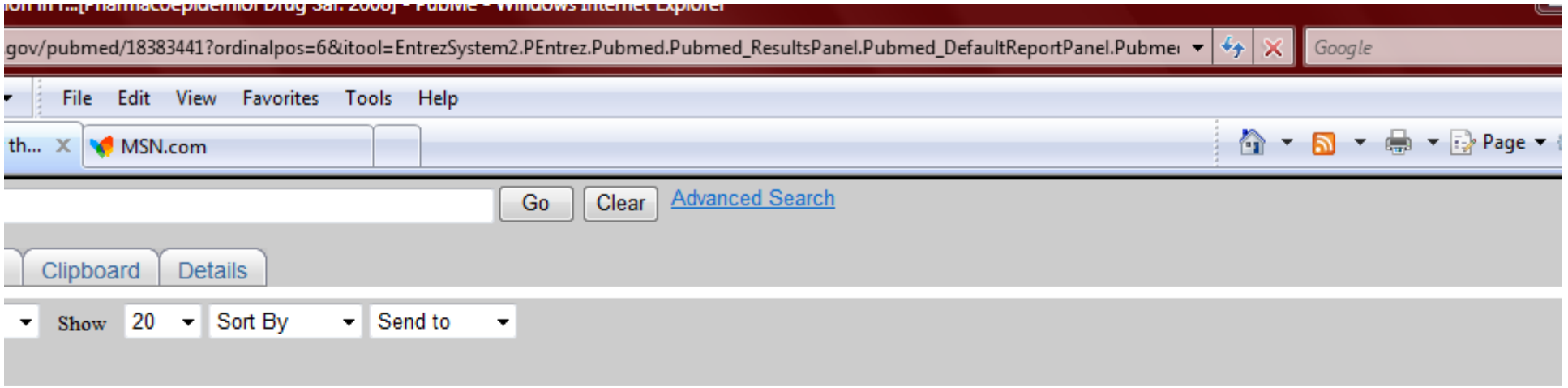

f. 2008 May;17(5):445-54.

FULL TEXT AVAILABLE ONLINE
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ecification in risk management plans: lessons learned from a pilot project.

CL, Evans SJ, Waller PC, Shakir S, Payvandi N, Murray AB.

d, Middlesex, UK. andrew.j.cooper@gsk.com

n of the ICH E2E guideline, risk management plans (RMP) defining the cumulative g limitations in safety information are now required for marketing authorisation ve research project was conducted to gain experience with tools for presenting y specification. This paper presents those tools found to be useful and the METHODS: Archive data from a successful MAA were utilised. Methods were extent of clinical safety experience, evaluating the sensitivity of the clinical fferences and identifying safety signals from adverse event and laboratory data nowledge with the drug. RESULTS: The extent of clinical safety experience was : exposure over time. Adverse event data were presented using dot plots, f patients with the events of interest, the odds ratio, and 95% confidence nterval plots were utilised for evaluating the sensitivity of the clinical database Box and whisker plots were used to display laboratory data. CONCLUSIONS: fy new evidence-based methods for presenting and evaluating clinical safety an advance in the way safety data from clinical trials can be analysed and ses the importance of early and comprehensive planning of the safety package, f epidemiology data.

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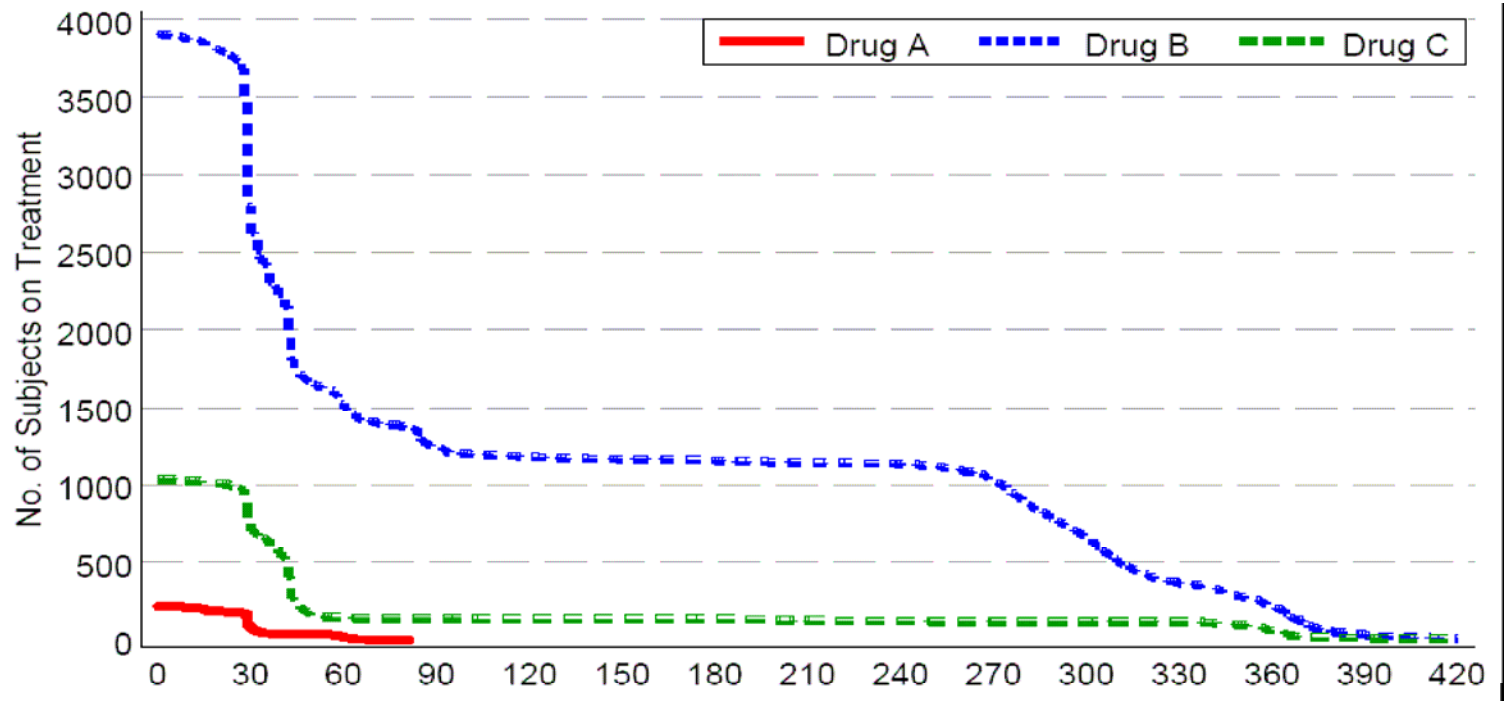
Extent of Clinical Safety Experience: Number of Patients Exposed by Time



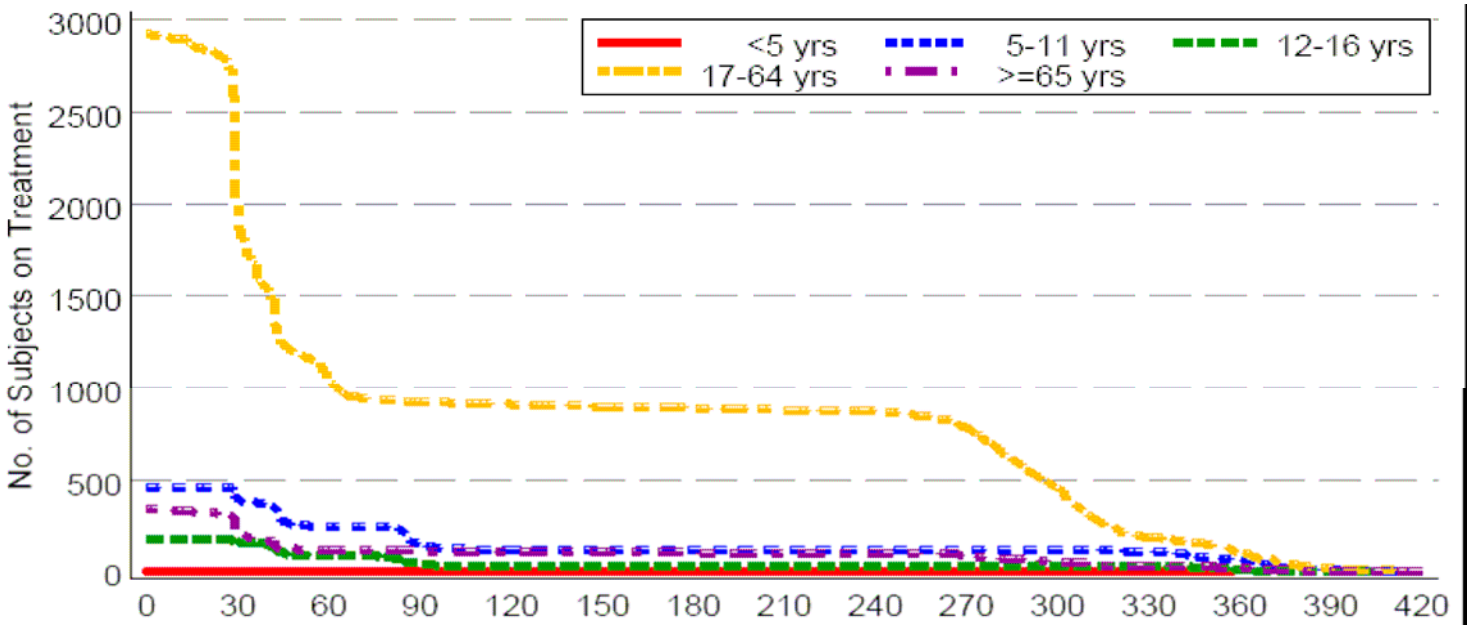
Subjects on Treatment

Drug A	213	17	0	0	0	0	0	0
Drug B	3904	1499	1175	1153	1130	663	212	11
Drug C	1036	142	135	132	121	119	62	7

During development based on intended numbers to be treated

- For duration of follow-up e.g. for vaccines

Extent of Clinical Safety Experience: Number of Patients Exposed by Time by Age- Group

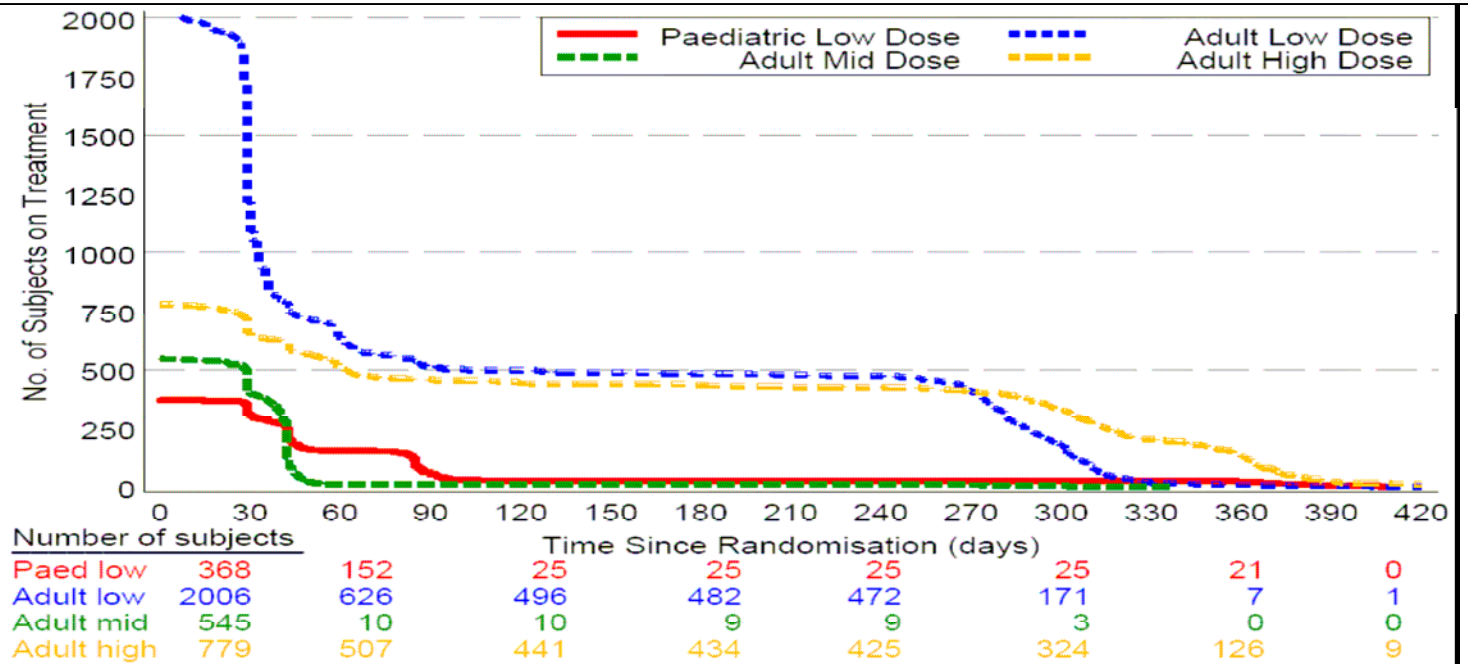


Number of subjects

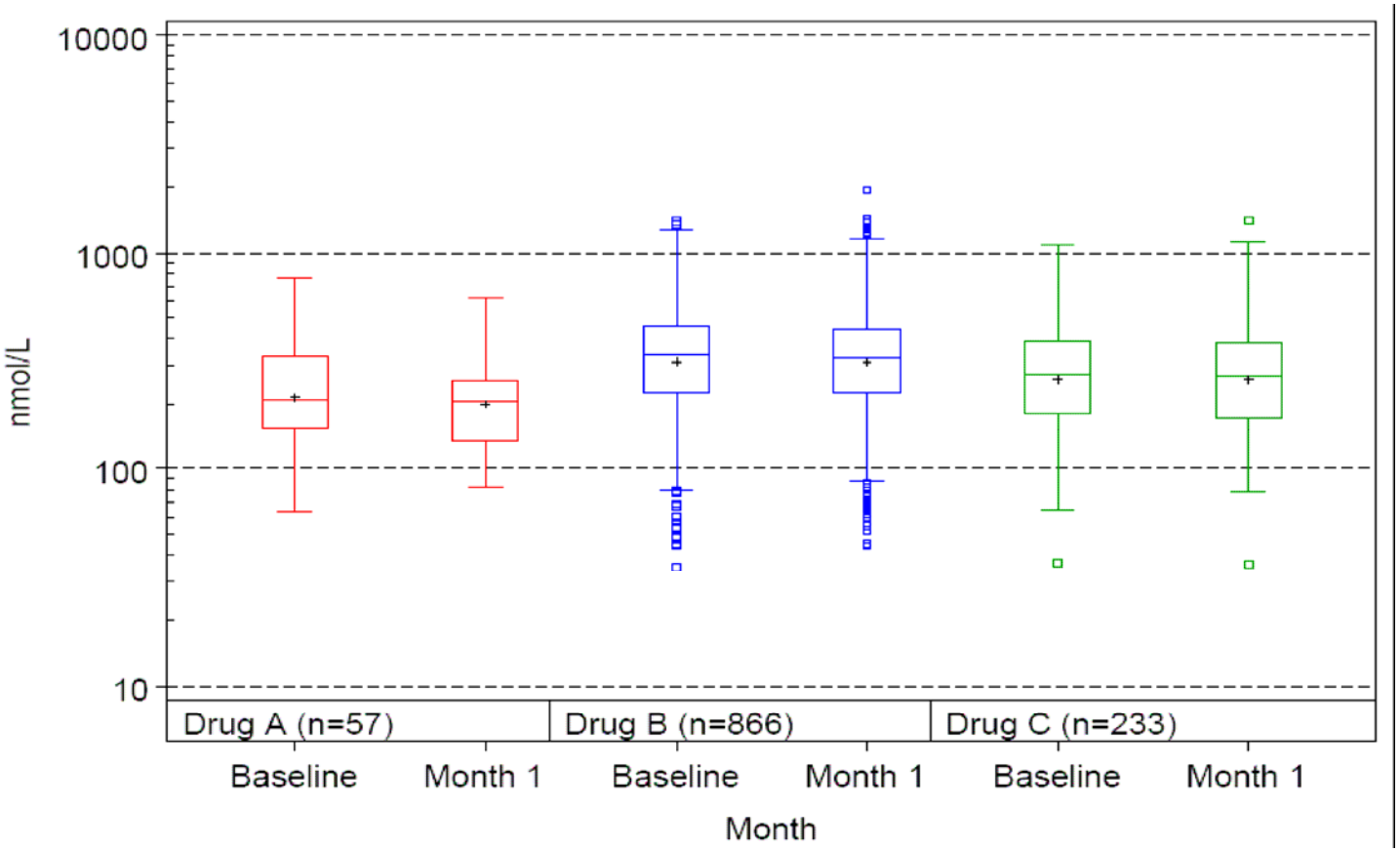
<5	2	1	1	1	1	1	0	0
5-11	462	250	122	122	122	121	63	1
12-16	176	90	35	35	34	34	17	0
17-64	2921	1039	908	888	869	451	109	8
>=65	339	119	109	107	104	56	23	2

Exposure plot can be produced:
By sub-groups e.g. age, gender, dose, study type (open-label v double-blind)

Extent of Clinical Safety Experience: Number of Patients Exposed by Time by Dose/Population



Displays of Laboratory Data: Box-Plot



Can use for absolute or change from baseline

Useful for identifying outliers for further investigation

Ivabradine - Modified PEM/Drug Utilisation Study

Ivabradine is licensed for the treatment for chronic stable angina pectoris in patients with a normal sinus rhythm, who have a contraindication or intolerance for beta-blockers

Ivabradine - Modified PEM/Drug Utilisation Study

To examine the utilisation of ivabradine

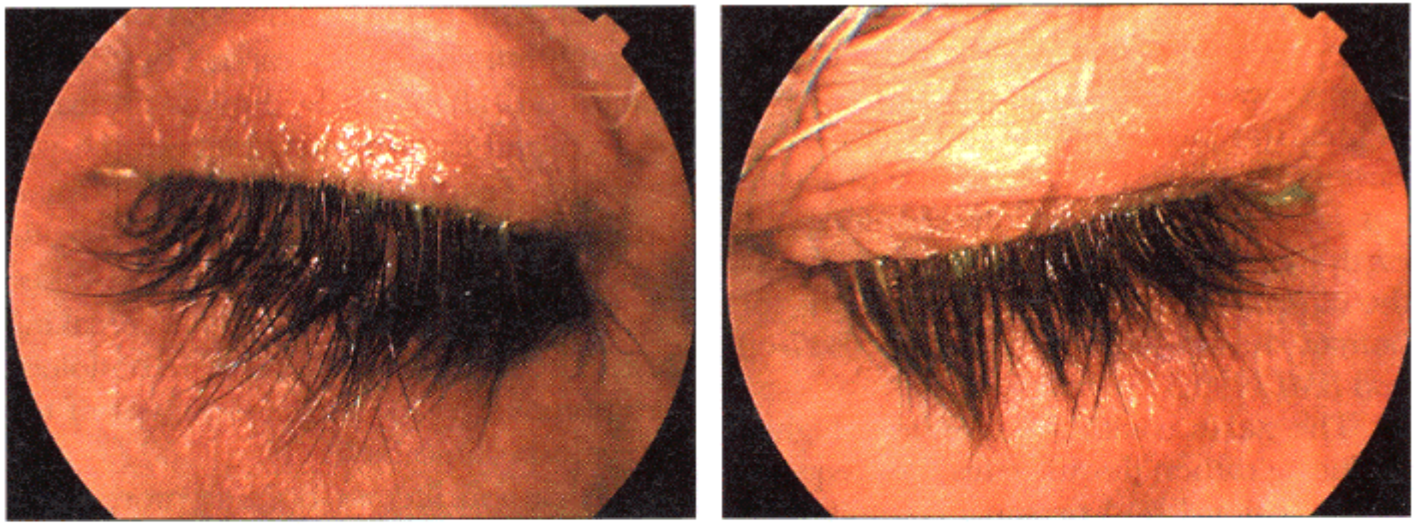
Specifically to investigate the use of ivabradine in relation to:

- Diseases/conditions that are contraindicated or a warning for use
- Pacemaker use
- Concomitant use of anti-anginal products (beta-blockers and nondihydropiridine calcium channel blockers)
- Concomitant use of CYP3A4 inhibitors and QT prolonging agents

The incidence and characteristics of phosphenes or blurring of vision, and persistent bradycardia will also be evaluated, as well as events given as reasons for stopping treatment.

Travaprost

- Prostaglandin analogue for treatment of open angle glaucoma
- Study to examine the safety of travaprost with specific emphasis on the incidence of four events:
  - Iris discoloration
  - Abnormal eye lash growth
  - Abnormal eyelid growth
  - Periocular skin disoloration
- Two questionnaires: 12 months and 24 months after first prescription (80.7% response rate)
- All the above eye events were reported uncommonly in the 24 months questionnaires



This 80 year old man presented with bilateral eyelash growth. Five years earlier, he had had primary open angle glaucoma diagnosed and was treated initially with levobunolol eye drops twice daily. These were changed to latanoprost eye drops at night to both eyes in order to improve his intraocular pressure control, and his condition had stabilised with this regimen for the previous three years. Latanoprost is a prostaglandin analogue and a common first line agent for treating open angle glaucoma. An increase in eyelash growth and eyelash density can occur with all classes of prostaglandin analogues as early as three weeks from the start of treatment. Reversal of growth on stopping treatment has been reported in some cases. This is an important side effect to consider when treating young patients with unilateral disease.

Shahram Kashani, *specialist registrar* (shahdoc@hotmail.com), Ashna Amin, *final year medical student*, Veronica Ferguson, *consultant*, department of ophthalmology, Charing Cross Hospital, London SE5 9RS

REMO Study

The Management and Outcomes of specific adverse drug reactions in patients prescribed rosiglitasone in primary care in England

L Wilton, P Biswas, S Harris, SAW ShakirISOP . Drug Safety.27;12

Follow-up forms

- Abnormal liver function tests
- Oedema
- Weight gain
- Cardiac failure
- Anaemia

Information on

- Medical history
- Concurrent medications
- Investigations
- How the event was detected and managed and its outcome

REMO Study

65% started by GPs and 33% by hospital doctors

The proportion that stopped treatment

- LFT abnormal 80%
- Anaemia 39%

Condition detected by routine monitoring

- Abnormal LFTs 87, 97%
- Anaemia 17, 65%
- Weight gain 100, 63%

But events which were detected when patients presented with a problem

- Cardiac failure 56, 70%
- Oedema 133, 54%

REMO study

GP managed

- Oedema 175, 71%
- Abnormal LFTs 58, 64%
- Weight gain 88, 56%

Patterns of interventions

- No actions taken for 68, 76% of abnormal LFTs
- Treatment with drugs for failure 55, 69%

REMO

Patients recovered

- Weight gain 72, 46%
- Cardiac failure 52, 65%

Patients did not recover

- Cardiac failure 8, 10%
- Abnormal LFTs 43, 48%

The Effects of Risk Management
Carvedilol in the treatment of heart failure
Interim report in 847 patients

Acharya N, Wilton LV, Shakir S. Int J Clin Pharmacol Ther.2005.43;1:1-6.

Treatment initiated by hospital specialists in 735 (87%)

Supervision under shared care 595 (70%)

>90% started carvedilol in the recommended dose

Grades of cardiac failure at start of treatment

- Grade II 281 37%
- Grade III 297 43%

On treatment with carvedilol

- improvement in NYHA was reported for 364 (43%)
- 20 <2.5% deteriorated

The type of evidence for safety used to support individual product withdrawals from the UK and/or US markets during the period 1999-2001. Drug Safety, Clarke A.,Shakir SAW

TYPE OF EVIDENCE \ DRUG	droperidol	cisapride	levacetylmethadol	phenylpropanolamine	pumactant	alosteron	rapacuronium	grepafloxacin	cerivastatin	astemizole	trogitazone
Animal studies	+	+	+	-	-	-	-	-	-	-	-
Spontaneous reports	+	+	+	+	-	+	+	+	+	-	-
Published case reports	-	-	-	-	-	-	-	-	-	-	-
Published case series	-	-	-	-	-	-	-	-	-	-	-
Cross-sectional study (of biomarker)	+	-	-	-	-	-	-	-	-	-	-
Case-control study	-	-	-	+	-	-	-	-	-	-	-
Cohort study	-	-	-	-	-	-	-	-	-	-	-
Non-randomised biomarker study	-	+	+	-	-	-	-	-	-	-	-
Randomised biomarker study	+	-	-	-	-	-	-	-	-	-	-
RCT	-	-	-	-	+	-	-	-	-	-	-
Other	-	-	-	-	-	+	+	-	-	-	-

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EUREKA! IT WON'T CURE ANYTHING, BUT THE SIDE EFFECTS ARE TERRIFIC!
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